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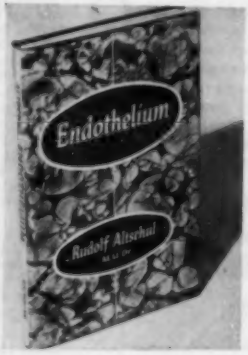

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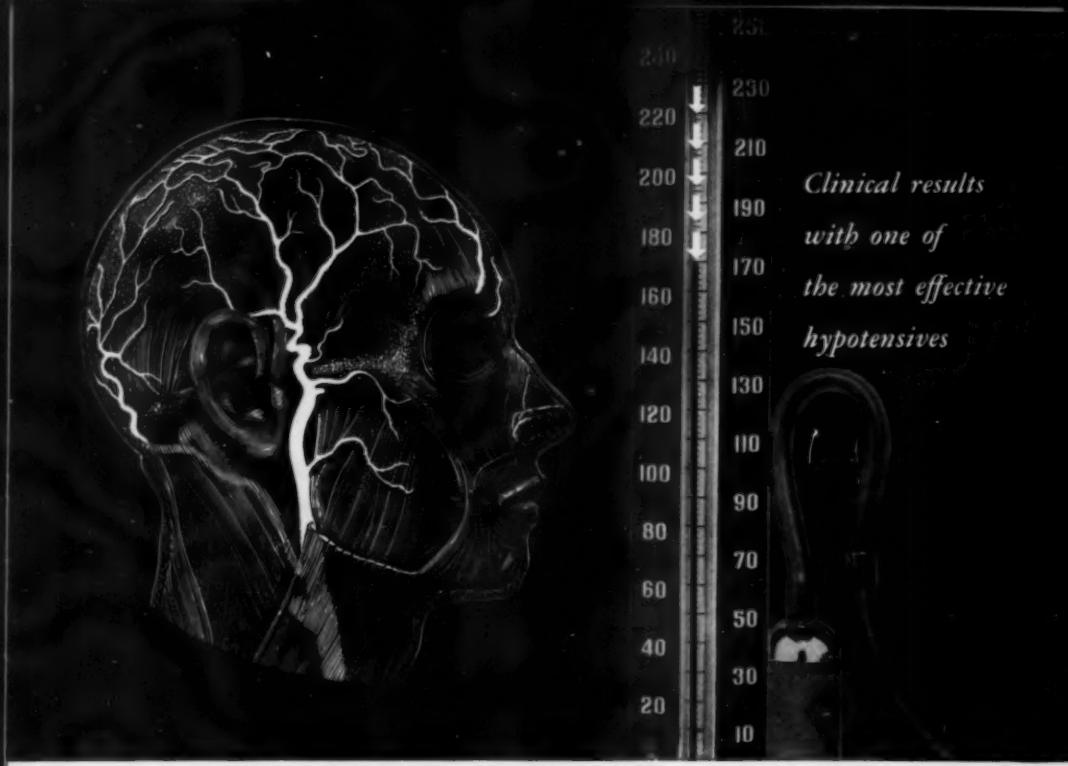

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2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.

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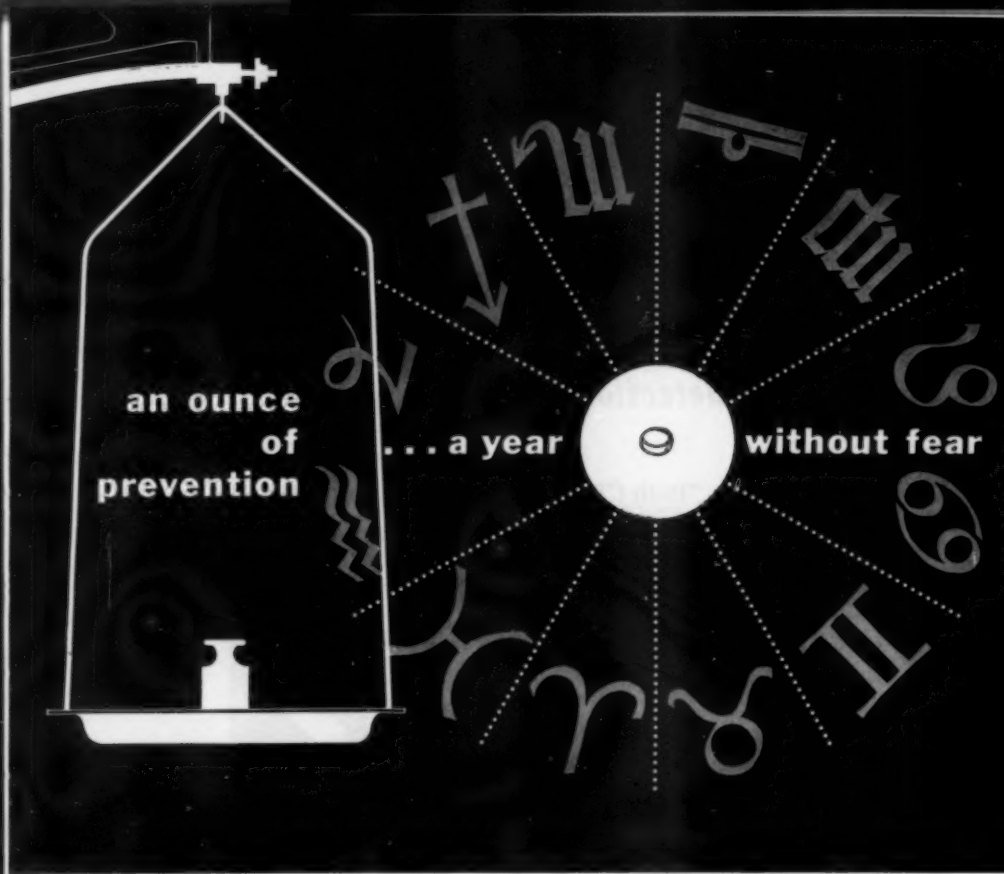

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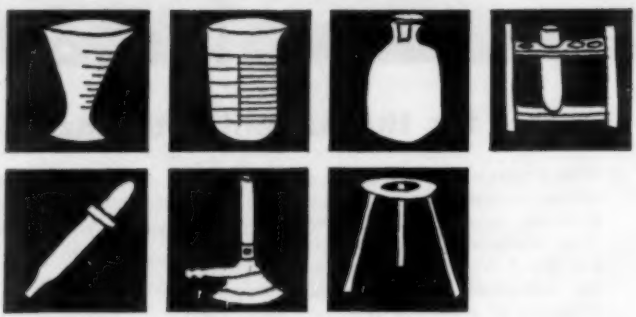

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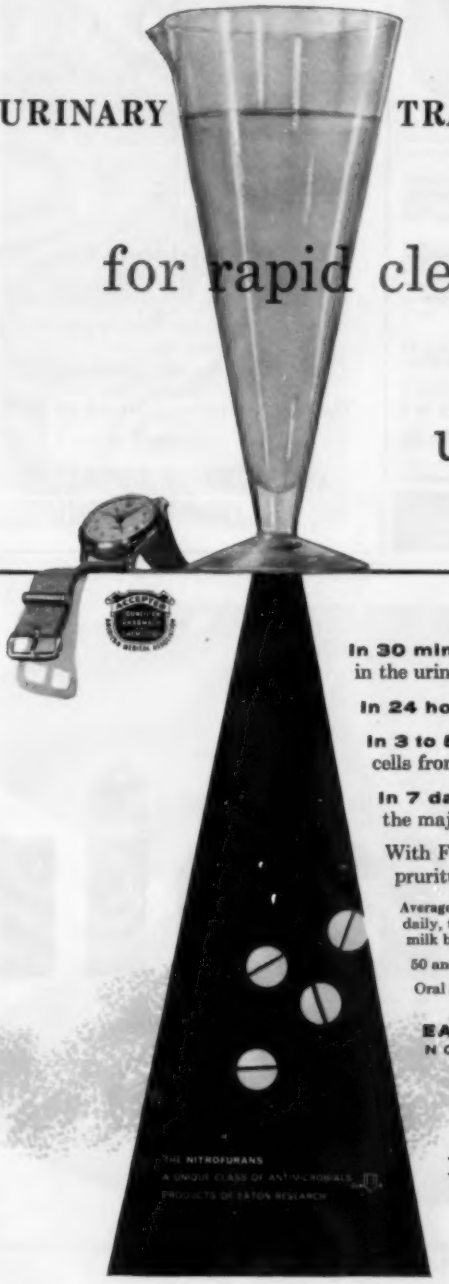

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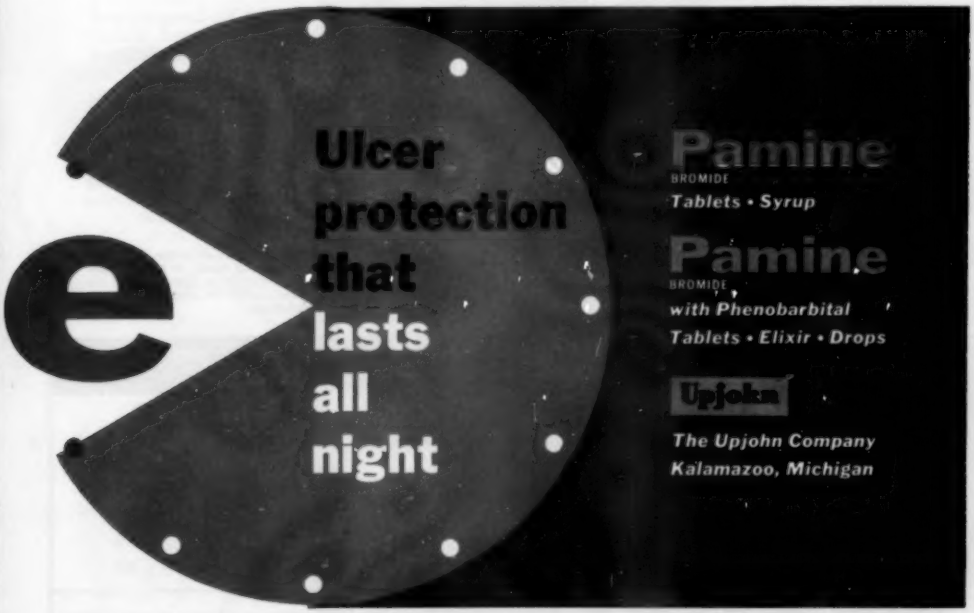

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, United States Department of Agriculture, Agricultural Handbook no. 8, 1950.
2. Data furnished by the Laboratories of The American Institute of Baking, Chicago, Illinois.
3. Sebrell, W.H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
4. Flour and Bread Enrichment, 1949-50, The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

B VITAMIN AND IRON CONTRIBUTION OF 5½ OUNCES* OF ENRICHED AND UNENRICHED BREADS AND PERCENTAGES OF RECOMMENDED DAILY ALLOWANCES**

	ENRICHED BREAD		UNENRICHED BREAD (of former years)	
	Amounts	Percentages of Recommended Daily Allowances	Amounts	Percentages of Recommended Daily Allowances
THIAMINE	0.37 mg.	25%	0.08 mg.	5%
NIACIN	3.40 mg.	23%	1.40 mg.	9%
RIBOFLAVIN	0.23 mg.	14%	0.09 mg.	6%
IRON	4.10 mg.	34%	1.10 mg.	9%

*An estimated amount of bread consumed daily by the average person.
**Daily dietary allowances (1953) recommended by the National Research Council for a fairly active man 45 years of age, 67 inches in height, and weighing 143 pounds.

AMERICAN BAKERS ASSOCIATION 20 NORTH WACKER DRIVE, CHICAGO 6, ILL.

in rheumatoid arthritis

adrenocortical hormone therapy can transform virtual helplessness into active ambulation

Cortril

tablets

brand of hydrocortisone

available as scored tablets, 10 mg. and 20 mg.

also available

TERRA-CORTRIL* Topical Ointment
TERRA-CORTRIL* Ophthalmic Suspension
New, easier-to-write, easier-to-remember names

CORTRIL Topical Ointment

CORTRIL Acetate Ophthalmic Ointment

CORTRIL Acetate Aqueous Suspension for intra-articular injection

when dosage is adjusted to patient's minimum need, Cortril therapy is as safe as therapy with any modern dramatic agent

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

*brand of oxytetracycline and hydrocortisone

IN CANCER PATIENTS

THORAZINE*

—*relieves:*

intractable pain

by the potentiation of analgesics, narcotics and sedatives.

nausea and vomiting

due either to the malignancy or distress-producing therapy.

apprehension and anxiety

associated with cancer and thus promotes a sense of well-being.

From a study of 'Thorazine' in patients with far advanced cancer, Lucas et al. state:

"Favorable effects included relief of pain, muscle spasm, nausea, vomiting, dyspnea, cough, restlessness, apprehension . . . improvement in appetite, sleeping, strength, sense of well-being and decrease in need for narcotics."

Proc. Am. A. Cancer Research *1*:30 (April) 1954

Available in 10 mg., 25 mg. and 50 mg. tablets; 25 mg. ampuls (1 cc.) and 50 mg. ampuls (2 cc.).

Additional information on 'Thorazine' is available on request.

Smith, Kline & French Laboratories

1530 Spring Garden Street, Philadelphia 1

*Trademark for S.K.F.'s brand of chlorpromazine hydrochloride

Chemically it is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride.

CLINICAL REPORT ON ANSOLYSEN . . . NEW ANTIHYPERTENSIVE AGENT

ANSOLYSEN—pentolinium tartrate—is a potent ganglionic blocking agent which presents the advantage of comparative freedom from by-effects. This effective hypotensive agent is recommended for use in patients with moderate to severe hypertension.

Comparing the effects of hexamethonium and ANSOLYSEN in 27 patients with severe "fixed" hypertension, Freis and coworkers[1] observed:

ANSOLYSEN was approximately five times more potent than hexamethonium

ANSOLYSEN produced less tolerance

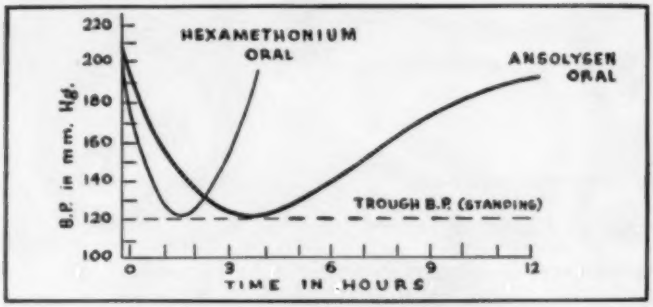
ANSOLYSEN's hypotensive effect was 40% longer

ANSOLYSEN's hypotensive effect was more predictable

ANSOLYSEN caused less pronounced by-effects

ANSOLYSEN caused less constipation

ANSOLYSEN lowered the blood pressure significantly, with little or no risk of producing collapse reactions or paralytic ileus



Changes in blood pressure noted by Smirk[2] after therapeutic oral doses of hexamethonium and ANSOLYSEN.

Supplied: Scored tablets—40 and 100 mg., bottles of 100
Injection—10 mg. per cc., vials of 10 cc.

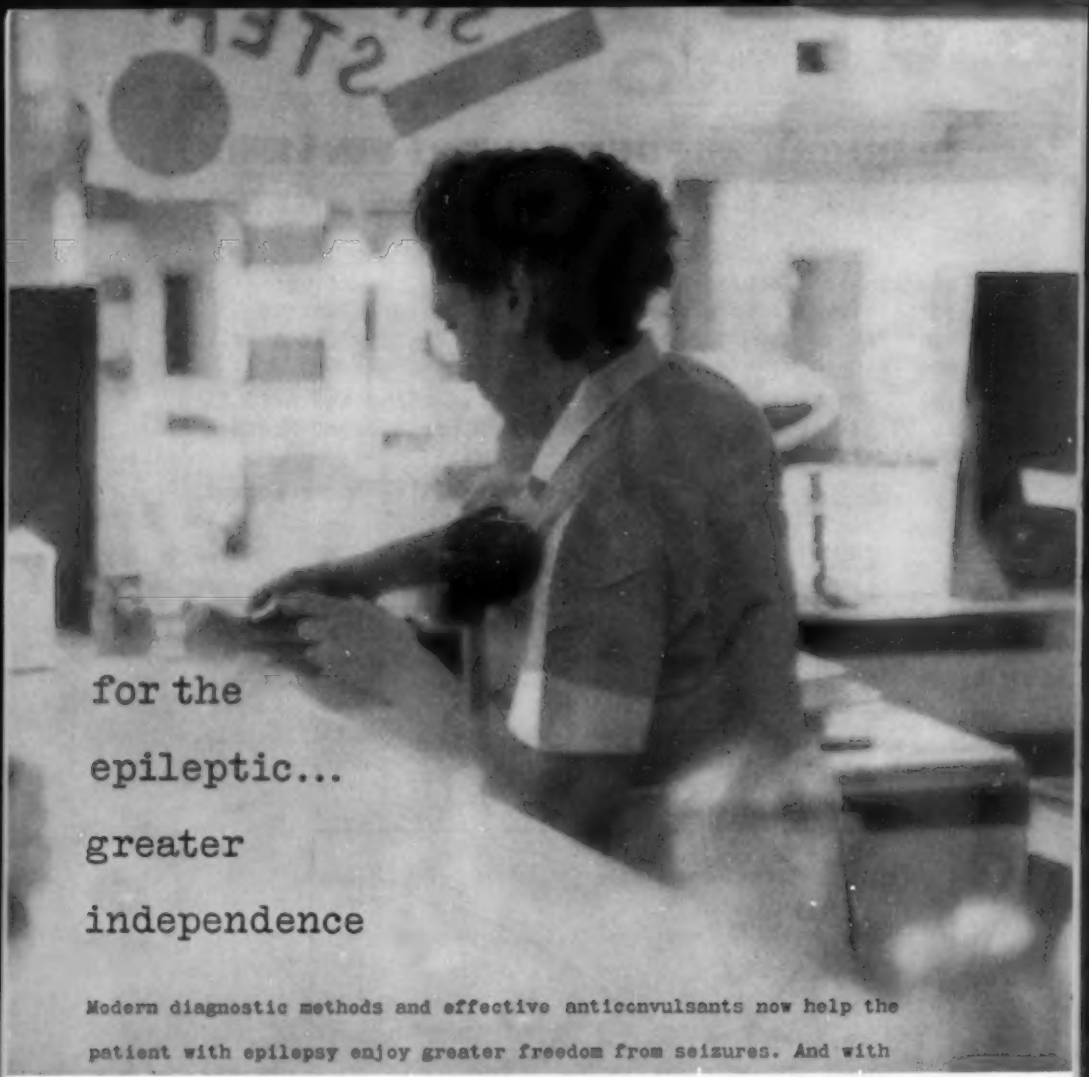
1. Freis, E. D., and others: Circulation 9:540 (April) 1954
2. Smirk, F.H.: New Zealand M.J. 52:1 (Oct.) 1953

ANSOLYSEN*

PENTOLINIUM TARTRATE

*Trademark

Wyeth
Philadelphia 2, Pa.



for the
epileptic...
greater
independence

Modern diagnostic methods and effective anticonvulsants now help the patient with epilepsy enjoy greater freedom from seizures. And with a more understanding society, greater independence is assured.

DILANTIN® SODIUM (diphenylhydantoin sodium, Parke-Davis)

an established anticonvulsant of choice, alone or in combination, for control of grand mal and psychomotor seizures -- without the handicap of somnolence.

DILANTIN Sodium is supplied in a variety of forms -- including Kapseals® of 0.03 Gm. (½ gr.) and 0.1 Gm. (1½ gr.) in bottles of 100 and 1,000.

Parke, Davis & Company

For every patient
with clearcut menopausal
symptoms such as **hot flushes,**
there's another patient with symptoms less clearly defined
yet just as distressing . . . headaches,
insomnia, mental and physical fatigue.
Her symptoms may also be indicative of declining ovarian function, and occur
several years before, and even long after, menstruation ceases.
This patient, too, may be expected to **benefit** from "Premarin" therapy.

"PREMARIN"® is a complete equine estrogen-complex.
It not only produces prompt symptomatic relief, but also imparts
a distinctive **"sense of well-being"**
highly gratifying to the patient. It is tasteless and odorless.
"Premarin," estrogenic substances (water-soluble),
also known as conjugated estrogens
(equine), is supplied in tablet
and liquid form.

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New York, N. Y. · Montreal, Canada

5401

NOW the safest agent yet developed for decisive control of BLOOD PRESSURE with 5 important firsts

UNITENS

brand of cryptenamine

Unitensen is recommended for the patient who needs more than tranquilizing effects. It produces positive, sustained falls in blood pressure.

This is what Unitensen Tablets do . . . and with unparalleled safety

Summary of Case Histories-Series A*

Age—Sex	BP—mm. Hg. BEFORE	BP—mm. Hg. AFTER
64—M	190/115	140/90
37—M	200/130	130/85
48—M	230/140	140/100
46—M	220/140	160/110
41—M	210/140	155/110
43—M	200/120	160/110
26—M	230/130	180/120
44—M	220/130	175/120
46—M	220/120	162/90

These patients experienced sustained control of blood pressure levels over prolonged periods of time.

(Write for complete clinical data, including case histories.)

*Personal communication to Irwin, Neisler & Company.

FIRST IN MAINTAINING DECISIVE BLOOD PRESSURE CONTROL

The sole therapeutic agent in Unitensen Tablets is cryptenamine —a potent blood pressure lowering alkaloid fraction isolated by the research staff of Irwin, Neisler & Company. In the majority of cases (see chart at left), cryptenamine will lower blood pressure decisively, and will control blood pressure at the lower levels for prolonged periods of time.

FIRST IN SAFETY

Unitensen Tablets exert a central action on the blood pressure lowering mechanism. Circulatory equilibrium is not disrupted. Improved circulation and improved work of the heart are often attained, *along with the decisive fall in blood pressure.*

Unitensen Tablets have no sympatholytic or parasympatholytic action. Ganglionic blocking does not occur. Unitensen Tablets *do not* cause postural hypotension and collapse, an ever-present risk with other potent blood pressure lowering drugs. Renal function is *not* impaired.

EN®

TANNATE TABLETS

Bottles of 50, 100, 500 and 1000.

FIRST WITH DUAL ASSAY

Unitensen is biologically standardized twice, first for hypotensive response and, second, for side effects (emesis) in the dog so that a safe therapeutic range between the two is assured. In extensive clinical trials only a few isolated cases exhibited occasional vomiting.

Unitensen Tablets do not cause the serious side effects common to widely used synthetic hypotensives. Unitensen Tablets can be given over long periods of time with entire dependability. Cumulative effects have not been noted.

FIRST IN SIMPLE DOSAGE

Start with 2 tablets daily, given immediately after breakfast and at bedtime. If more tablets are needed, include an afternoon dose at 1 or 2 p.m.

FIRST IN ECONOMY

Because of lower dosage, Unitensen Tablets save your patients ⅓ to ½ over the cost of other potent blood pressure lowering agents.

Each Unitensen Tablet contains: Cryptenamine*..... 2 mg.†
(as the tannate salt)

*Ester alkaloids of Veratrum viride obtained by an exclusive Irwin-Neisler nonaqueous extraction process. †Equivalent to 260 Carotid Sinus Reflex Units.

IRWIN, NEISLER & COMPANY DECATUR, ILLINOIS

four good things happen to your peptic ulcer patient when Kolantyl goes to work

Painful gastrointestinal spasm is relieved · hyperacidity is neutralized · cellular repair is encouraged · mechanical erosion is arrested (1). Give your next ulcer patient economical 4-way relief. Prescribe pleasant-tasting KOLANTYL GEL.

(1) Johnston, R. L.: J. Ind. St. Med. Assn. 46:869, 1953
(2) McHardy, G. and Browne, D.: Sou. Med. J. 45:1139, 1952

Merrell
Since 1828

Kolantyl Gel

Rx INFORMATION

Action:

1. Bentyl* combines spasmolysis and parasympathetic-depressant actions without the side effects of atropine.
2. Prompt, prolonged neutralization of excess gastric acidity... magnesium oxide and aluminum hydroxide.
3. Protective, demulcent coating action over the ulcerated area ...methylcellulose.
4. Checks the mucus-destroying action of lysozyme and pepsin... sodium lauryl sulfate.

*Merrell's distinctive antispasmodic that is more effective than atropine —free from side effects of atropine.[2]

Composition: Each 10 cc. of Kolantyl Gel or each Kolantyl tablet contains:

Bentyl Hydrochloride . .	5 mg.
Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate .	25 mg.
Methylcellulose	100 mg.

Dosage: Gel—2 to 4 teaspoonfuls every three hours, or as needed. Tablets—2 tablets (chewed for more rapid action) every three hours, or as needed.

Supplied: Gel—12 oz. bottles. Tablets—bottles of 100 and 1,000.

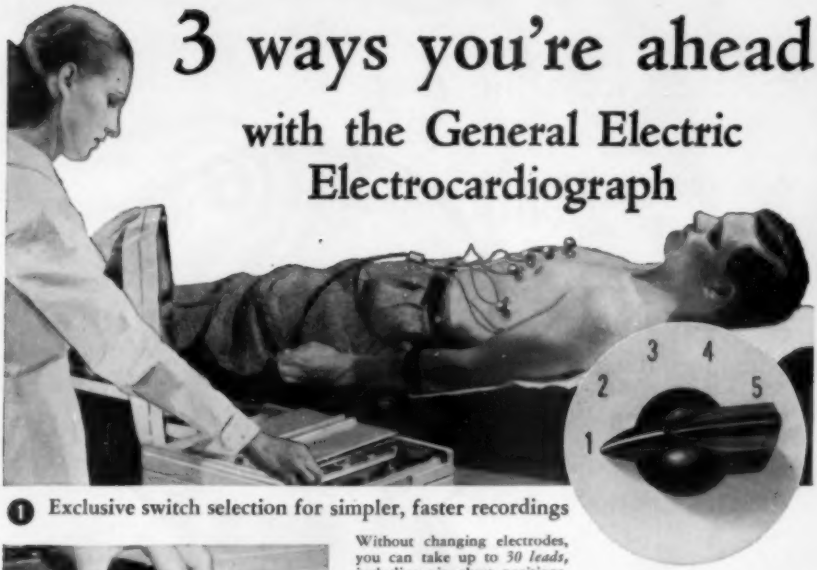
T. M. Kolantyl®, 'Bentyl'.

The Wm. S. Merrell Company
CINCINNATI
New York • St. Thomas, Ontario

PIONEER IN MEDICINE FOR OVER 125 YEARS

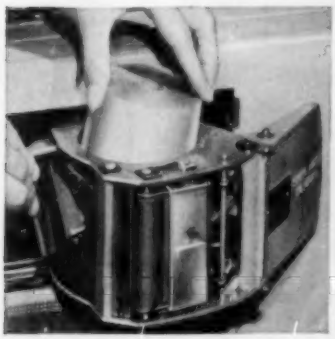
3 ways you're ahead

with the General Electric Electrocardiograph



1 Exclusive switch selection for simpler, faster recordings

Without changing electrodes, you can take up to *30 leads*, including six chest positions. Once the patient electrodes are in place, you can take leads 1, 2, 3, aVR, aVL, aVF, and the 1 to 6 positions at V, CR, CL and CF by merely turning selector switches.



2 New paper drive for easier loading, greater accuracy

Using a new type of roller and a synchronous motor, General Electric assures uniform paper speed for accurate measurement of conduction times. Loading is simple — nothing to disassemble. Just flip open hinged door . . . place paper roll on spindle . . . thread through simple guides . . . and snap unit back in place. *All in a few seconds.*

3 New cabinet design for easier operation and carrying, added safety

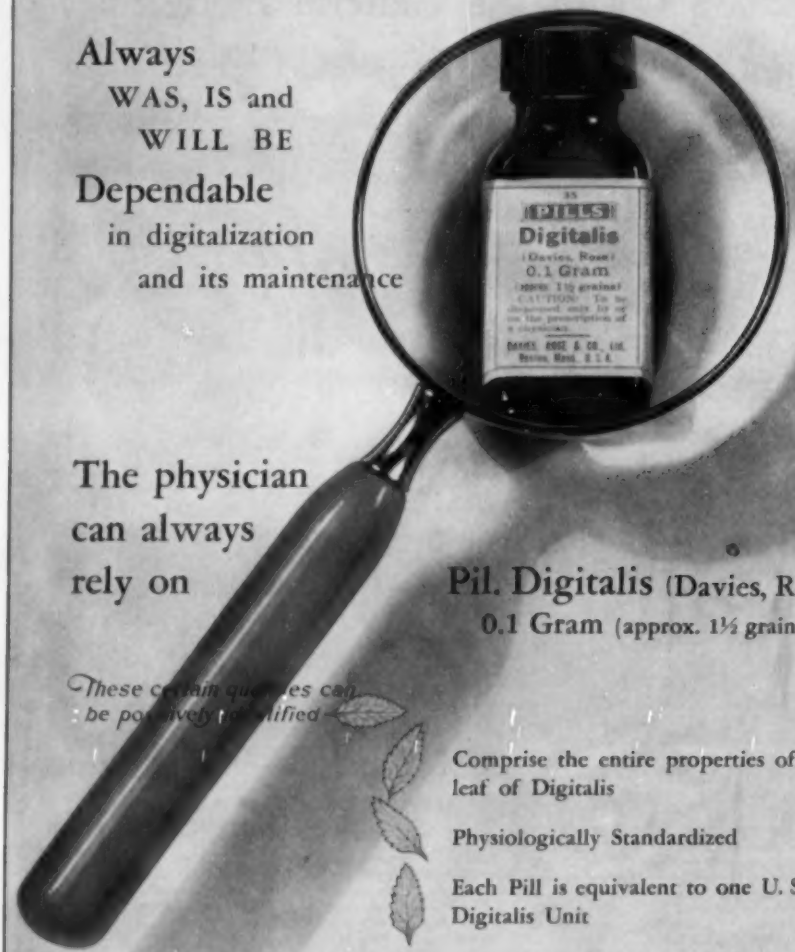
Dual hinged covers open at a touch, making recessed controls immediately accessible. Cover supports no weight when unit is carried — handle attaches to main case. For all the facts on the DWB Cardioscribe, see your G-E x-ray representative. Or write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-115.

Progress Is Our Most Important Product

GENERAL ELECTRIC

Made from the *leaf*—

Always
WAS, IS and
WILL BE
Dependable
in digitalization
and its maintenance



The physician
can always
rely on

Pil. Digitalis (Davies, Rose)
0.1 Gram (approx. 1½ grains)

These certain qualities can be positively identified

Comprise the entire properties of the leaf of Digitalis

Physiologically Standardized

Each Pill is equivalent to one U. S. P. Digitalis Unit

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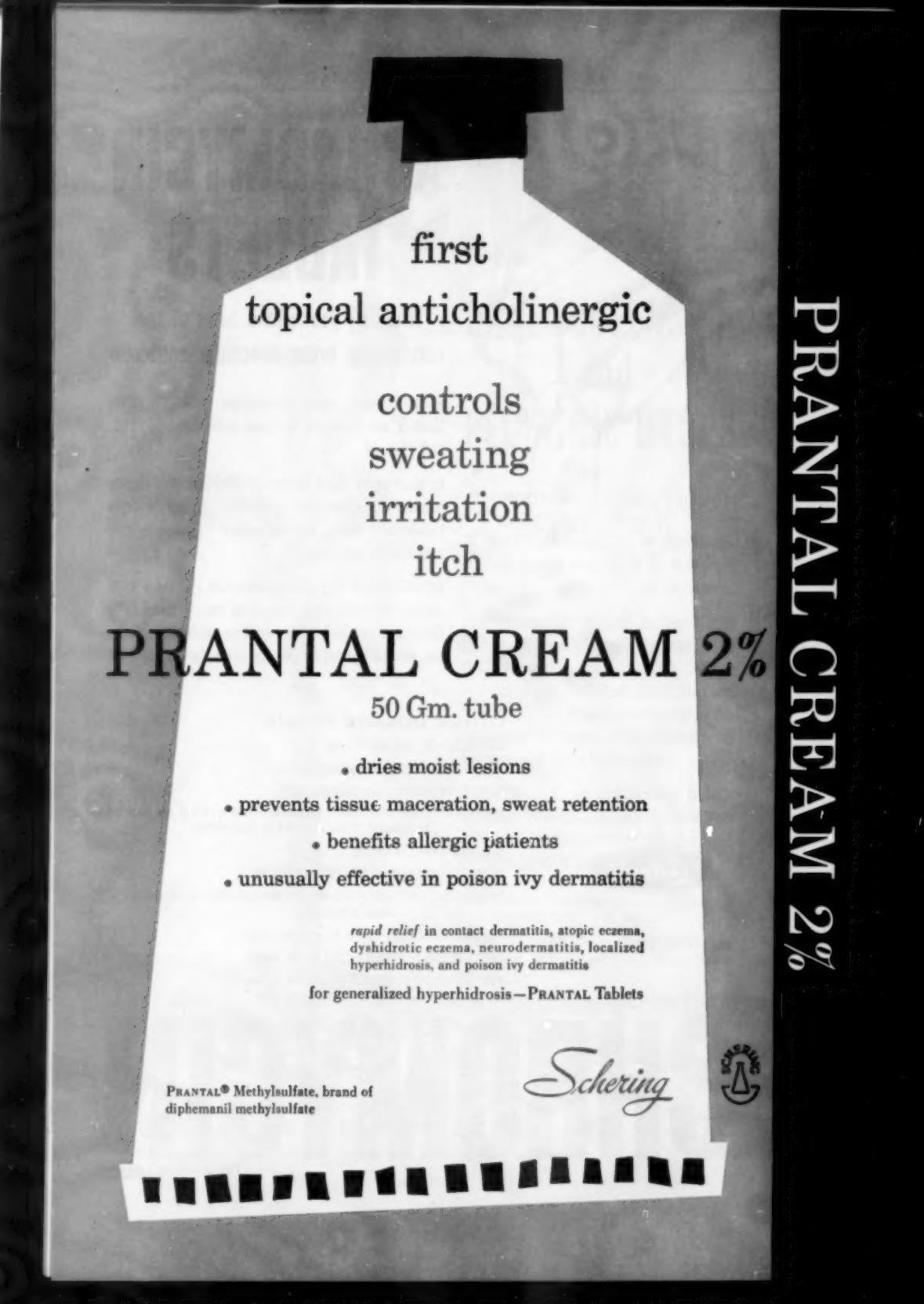
PHARMACEUTICAL MANUFACTURERS

D23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topical anticholinergic
controls
sweating
irritation
itch
PRANTAL CREAM 2%
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• dries moist lesions
• prevents tissue maceration, sweat retention
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rapid relief in contact dermatitis, atopic eczema, dyshidrotic eczema, neurodermatitis, localized hyperhidrosis, and poison ivy dermatitis
for generalized hyperhidrosis—PRANTAL Tablets
PRANTAL® Methylsulfate, brand of diphemanil methylsulfate
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SCHERING
PRANTAL CREAM 2%

ACHROMYCIN
TETRACYCLINE
TABLETS

A widely prescribed form of the outstanding broad-spectrum antibiotic

Sugar-coated, easy-to-swallow ACHROMYCIN Tablets are available in three potencies: 50, 100, and 250 mg.

In each of its many forms, ACHROMYCIN exhibits notable characteristics: it diffuses rapidly in body tissues and fluids; gastrointestinal irritation is rare and mild in nature.

ACHROMYCIN has proved effective against a wide variety of infections including those caused by Gram-positive and Gram-negative bacteria, rickettsia, and certain virus-like and protozoan organisms.

OTHER DOSAGE FORMS

CAPSULES: 50, 100, and 250 mg.

PEDIATRIC DROPS: (see opposite page)

ORAL SUSPENSION: (see opposite page)

SPERSOIDS* Dispersible Powder (Chocolate Flavor): 50 mg. per rounded teaspoonful (3 Gm.), 12 and 125 dose bottles

SOLUBLE TABLETS: 50 mg.

INTRAVENOUS: vials of 100, 250, and 500 mg.

INTRAMUSCULAR: vials of 100 mg. (for dilution with 2 cc. of sterile water or saline)

TOPICAL OINTMENT (3%): ½ and 1 oz. tubes

OPHTHALMIC OINTMENT (1%): ⅛ oz. tubes

EAR SOLUTION (0.5%): 10 cc. dropper bottles

*REG. U.S. PAT. OFF.

Lederle

ACHROMYCIN*

Tetracycline Lederle

ACHROMYCIN*

Tetracycline Lederle

ORAL SUSPENSION and PEDIATRIC DROPS

popular cherry flavor

ACHROMYCIN is available in two cherry-flavored dosage forms that are highly acceptable to patients—particularly children.

The Pediatric Drops are packaged with an easy-to-read graduated dropper. The Oral Suspension, supplied as dry crystals in a 1 oz. bottle. Both Oral Suspension and Pediatric Drops, when reconstituted by the pharmacist or nurse, retain potency for two weeks at room temperature.

ACHROMYCIN, an outstanding broad-spectrum antibiotic, is relatively free from untoward side reactions and provides rapid diffusion in body tissues and fluids.

ORAL SUSPENSION (Cherry Flavor): 250 mg. per teaspoonful (5 cc.), 1 oz. bottles

PEDIATRIC DROPS (Cherry Flavor): 100 mg. per cc. (approx. 5 mg. per drop), 10 cc. bottles

*REG. U.S. PAT. OFF.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY PEARL RIVER, N.Y.

Lederle

Viso-Cardiette Interpretation

Only an *accurate* electrocardiogram will provide the physician or cardiologist with the true information that he seeks. And from the abnormalities of a 'cardiogram the abnormalities of the corresponding portions of the heart can be read. Likewise Viso records present a 'cardiographic pattern which mirrors the true worth of the instrument.

Performance of the Viso means the extremely simplified manner in which records are obtained. Routine testing time, patient connection included, averages about seven minutes.

Quality of appearance of the Viso is an outward indication of a quality within. And its inward quality of construction conduces to the Sanborn *quality of results.*

Reliability of the Viso is practically assured by the Sanborn background of over *thirty years* of ECG design and manufacture. Simply ask any Viso owner about Viso!

Service by Sanborn is something to be sure of. A network of offices includes *thirty* in centrally located cities throughout the country, and exclusive Service Helps by mail are available to *every* owner.

Trial Plan the Viso way means your privilege to test a machine *in your* practice for 15 days *without any obligation whatsoever.* Write for details and descriptive literature.

SANBORN COMPANY
195 Massachusetts Avenue, Cambridge 39, Massachusetts

full therapeutic effects of aminophylline - ORALLY

for:

BRONCHIAL AND CARDIAC ASTHMA

CONGESTIVE HEART FAILURE

PAROXYSMAL DYSPNEA

EDEMATOUS STATES

AMINODROX-FORTE supplies aminophylline, combined with a specially prepared aluminum hydroxide which minimizes gastric irritation, yet permits rapid absorption. Daily ORAL dosage can be tolerated to produce and maintain the constant, high blood levels necessary for effective therapy.

AMINODROX-FORTE, containing 3 gr. of Aminophylline, permits dosage flexibility. Smaller, frequently repeated doses provide sustained therapeutic blood levels and further diminish the incidence of undesirable side reactions.

AMINODROX® - FORTE

each Aminodrox-Forte tablet contains:

aminophylline ..... 3 gr.
Aluminum Hydroxide Gel, dried ..... 4 gr.

used for professional literature and samples

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE

. . . a "confused" old lady

'Dexamyl' helped

. . . an extremely nervous man

(Photographs and excerpts of care histories from the files of a general practitioner.)

Remember: 'Dexamyl' is now available in the unique 'Spansule' capsule dosage form—to provide smooth, prolonged, uninterrupted mood-ameliorating effect for a period of 10-12 hours—*with just one oral dose.* 'Dexamyl' *Spansule* capsules are available in two strengths (see lower right, facing page).

Patient S. M. (80) was "plagued with nervousness, profound weakness, vertigo, and pain . . . add to this the untimely catastrophic death of a daughter."

'Dexamyl' relieved "her nervous uncertainty, her depressive weariness, her melancholia, and her tearfulness . . . also her vertigo . . . 'Dexamyl' helped her to smile again."

Patient L. H. (51) "had positive tremors of the eyelids, tongue, fingers, lips and voice . . . His complaints always centered about extreme nervousness, jitteriness, depression, and 'all-gone weakness'.

" 'Dexamyl' allayed inward tension . . . gave him a sensation of amelioration and comfort . . . Yet, even in this intensely irritable patient, there were no side effects . . .

"He is now able to work and support himself, which he was unable to do for several years."

Dexamyl*

tablets—elixir—Spansule† capsules

relieves both anxiety

and depression—promotes

a feeling of composure

'Dexamyl' provides the synergistic action of two mood-ameliorating components: 'Dexedrine' and amobarbital.

Tablets—each containing Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital, ½ gr. (32 mg.).

Elixir—each teaspoonful (5 cc.) equivalent to one Tablet.

'Dexamyl' ***Spansule*** **(No. 1)**—each containing the equivalent of *two* tablets: 'Dexedrine' Sulfate, 10 mg.; amobarbital, 1 gr. (65 mg.).

'Dexamyl' ***Spansule*** **(No. 2)**—each containing the equivalent of *three* tablets: 'Dexedrine' Sulfate, 15 mg.; amobarbital, 1½ gr. (97 mg.).

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of sustained release capsules (patent applied for).

"A program of treatment for *chronic ulcerative colitis...*

as described by Lester M. Morrison, M.D., Los Angeles[1]

...is based on the use of 1) azopyrine*, 2) ACTH or cortisone and 3) psychotherapy."

"Azopyrine* ... has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."

1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

*now available under the name...

Azulfidine®

BRAND OF SALICYLAZOSULFAPYRIDINE

Reports on Azulfidine:

(This drug has been presented under three different names, which appear in the literature cited, viz: Salazopyrin, Azopyrin and the now established name in America, Azulfidine.)

1949 "The administration of salicylazosulfapyridine (salazopyrin) produced marked improvement in 8 of 12 cases of ulcerative colitis."

Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases."

Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

literature on request from

PHARMACIA LABORATORIES, Inc.

Executive Offices: 270 Park Ave., New York 17, N. Y., Sales Offices: 300 First St., N.E. Rochester, Minn.

IN TENSION AND HYPERTENSION

sedation without hypnosis

℞ Serpasil T. M.

(reserpine CIBA)

A pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

In anxiety, tension, nervousness and mild to severe neuroses—**as well as in hypertension**—SERPASIL provides a nonsoporific tranquilizing effect and a sense of well-being. Tablets, 0.25 mg. (scored) and 0.1 mg.

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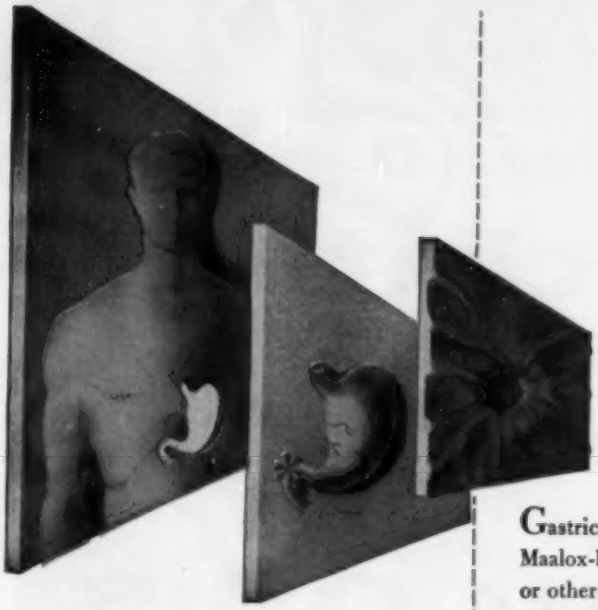

maalox.®

gives ulcer relief

without side effects

Gastric hyperacidity is controlled by Maalox-Rorer without constipation or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

Supplied: in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

Samples will be sent promptly on request.

WILLIAM H. RORER, INC.
Drexel Bldg., Independence Square
Philadelphia 6, Pa.

Clinicopharmacologic Properties of Gitaligin®

[Brand of Amorphous Gitalin]

The following table is quoted verbatim from the report by Dimitroff, S.P.; Griffith, G.C.; Thorner, M.C. and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure, Annals Int. M. 39:1189 (Dec.) 1953.

Derivation	*Digitalis purpurea.*
Appearance	Amorphous white powder.
Uniformity	Constant from batch to batch.
Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
Dissipation	Rate of excretion between the rapidly excreted Digoxin and slowly excreted leaf or digitoxin.
Range of toxicity	Less toxic than other glycosides. Digitalizing dose is about 1/3 amount of the toxic dose.
Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4-6 hours until toxic or therapeutic effect appears (usually 24-48 hours.)
Dosage by slow method	A single dose of 1.5 mg. daily, or 0.5 mg. t.i.d. until toxic or therapeutic effect appears (usually 4-7 days).
Symptoms of toxicity	Same as for other glycosides, i.e., anorexia, nausea, vomiting, color-vision, ectopic beats, ST-T changes.

WHITE LABORATORIES, INC., Kenilworth, N.J.

Simple dosage equivalent: 0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf. Gitaligin is supplied in 0.5 mg. tablets, deep scored for accuracy and flexibility of dosage—in bottles of 30 and 100.

Gitaligin is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

compare before you prescribe

modern criteria of good digitalis therapy

1. pure active principle
2. complete absorption
3. rapid onset of action
4. smooth, even maintenance
5. frequent dosage readjustment unnecessary
6. virtual freedom from gastric upset

digitaline nativelle®

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

compare *then prescribe...*

DIGITALINE NATIVELLE

—the original pure crystalline digitoxin

Consult your Physicians' Desk Reference for dosage information.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

SUR-BEX®

(Abbott's Vitamin B Complex Tablets)

or SUR-BEX with Vitamin C

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1. Garrett, T. A.: Personal communication.

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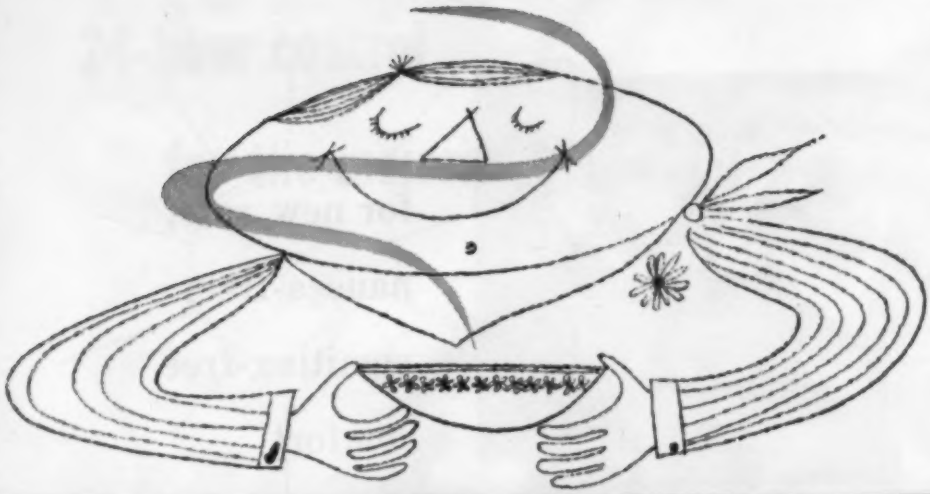

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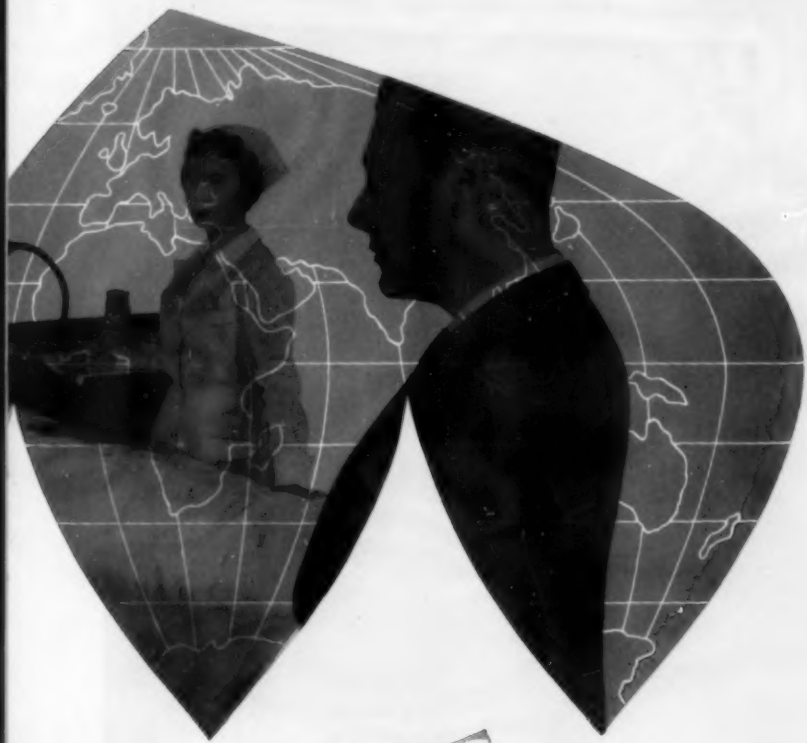

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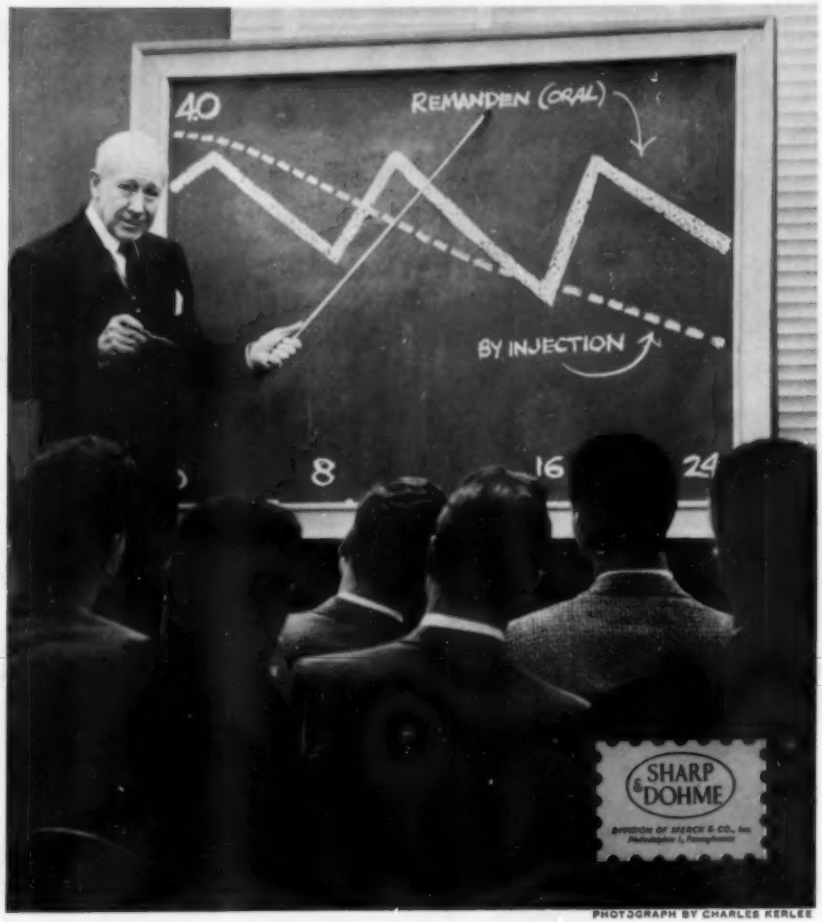

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ANNALS OF
INTERNAL MEDICINE

VOLUME 41 OCTOBER, 1954 NUMBER 4

CEREBRAL VASCULAR DISORDERS * †

By SIR RUSSELL BRAIN, F.A.C.P. (Hon.), *London, England*

THE number of deaths from vascular lesions of the nervous system in England and Wales is large and growing larger every year. According to the Registrar-General's figures, in 1942 the number was 56,048 and in 1952 it was 69,388, or approximately 14% of the total deaths. I have analyzed a series of 100 hospital patients admitted to the neurological department at the London Hospital and 100 patients seen in private consultation, all suffering from cerebral vascular disease, with special reference to their age distribution and the nature of their lesion and the correlation between the two. From the chart of the age distribution of the combined groups (figure 1) it will be seen that about half are over the age of 60 and about half are under this age, and about one quarter are below the age of 50. Hence, as Dr. Irving Wright points out, it would be a mistake to regard these disorders as predominantly afflicting the elderly and the aged. A substantial proportion of sufferers are in the prime of life. If now we separate the hospital patients from the private patients (figure 2) an interesting difference in age distribution appears. More of the hospital patients fall into the younger age groups and more of the private patients into the older age groups. Only 37% of the hospital patients are over the age of 60, whereas 67% of the private patients are over this age. The explanation of this is to be found in the fact that patients with acute cerebral vascular lesions tend to be admitted straight to hospital, and this includes many suffering from subarachnoid hemorrhage due to rupture of an intracranial aneurysm or angioma, who are younger than most patients suffering from the chronic effects of degenerative lesions of the cerebral vascular system, more of whom are seen in private consultation. This is shown in figure 3, where the age distribution of patients suffering from such de-

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.
† By special arrangement this paper will appear simultaneously in *The Lancet*.

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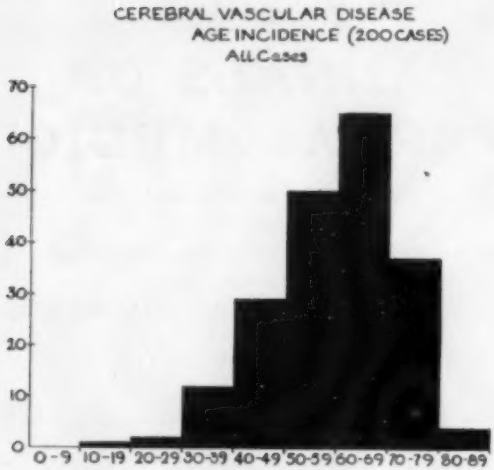


FIG. 1.

generative diseases is separated from that of those suffering from subarachnoid hemorrhage, angioma or aneurysm, the age distribution of which is also shown in figure 4.

Table 1 shows an analysis of the pathology in the 200 cases. The total amounts to more than 200 because some patients had more than one type of disorder. The first point which attracts attention is the substantial

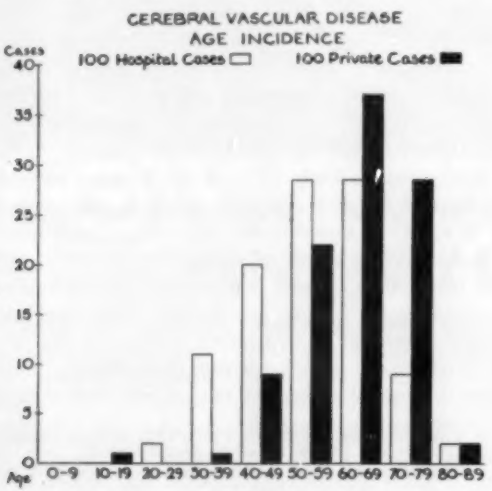
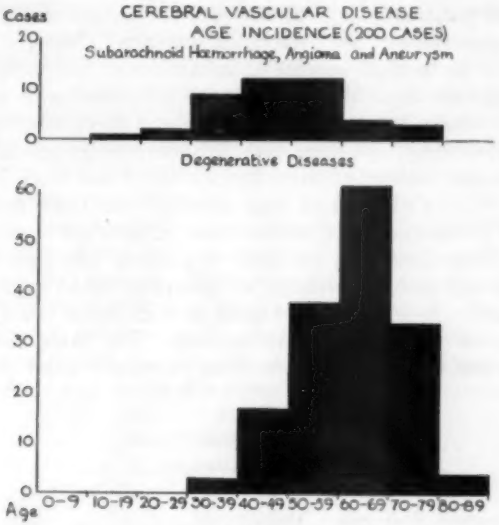


FIG. 2.


CEREBRAL VASCULAR DISEASE
AGE INCIDENCE (200 CASES)
Subarachnoid Haemorrhage, Angioma and Aneurysm
Cases
20
10
0
Degenerative Diseases
60
50
40
30
20
10
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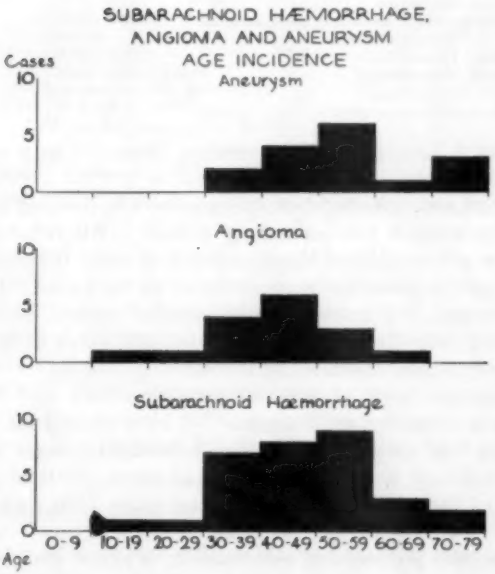
Age
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89

FIG. 3.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Cases
Aneurysm
10
5
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Angioma
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5
0
Subarachnoid Haemorrhage
10
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Age
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FIG. 4.

proportion of patients (16% of the total) who suffered from either an intracranial aneurysm or an intracranial angioma. Many of these patients were admitted to hospital because of subarachnoid hemorrhage, which, especially in the case of an angioma, may be associated with an intracerebral hemorrhage. Some patients with an angioma were admitted for the investigation of epilepsy, and some with an aneurysm because of the symptoms of focal pressure. Most of these lesions could not have been diagnosed during life without the aid of angiography, and their detection by this method is of great importance because some of them are amenable to surgical treatment. In the majority of cases of patients admitted to hospital because of subarachnoid hemorrhage, an aneurysm or an angioma was found to be the cause. In a minority of cases no such lesion could be detected on angiography, or angiography was refused. The three cases of cerebral embolism in the series were the result of rheumatic heart disease: like Dr.

TABLE 1

Cerebral Vascular Disease

200 Cases

Diagnoses			Total	Per Cent
Intracranial Aneurysm	Verified	10	16	8
	Suspect	6		
Intracranial Angioma	Verified	13	16	8
	Suspect	3		
Subarachnoid Hemorrhage			30	15
Cerebral Embolism			3	1.5
Migraine, with Permanent Hemianopsia			5	2.5
Cerebral Arteriosclerosis			77	38.5
Cerebral Infarction			47	23.5
Cerebral Hemorrhage			6	3
Benign Hypertension			96	48
Malignant Hypertension			3	1.5

Irving Wright, I have encountered cerebral embolism as a complication of operation on the heart.

The five patients suffering from permanent hemianopsia as the result of migraine form a small but interesting group. This occurrence has been recognized for a long time. Angiography has made it possible to exclude an aneurysm of the posterior cerebral artery as the cause. In such cases I have had instances of a failure of the posterior cerebral on one side to fill on angiography, and the most likely explanation seems to be that a spasm of this artery has been followed by thrombosis.

The distinction between cerebral arteriosclerosis and "focal cerebral infarction" is a somewhat arbitrary one. I have applied the term "cerebral arteriosclerosis" to those patients whose cerebral lesions were evidently due to arteriosclerotic ischemia, but who had not at any time presented signs of a substantial focal lesion. I have classed those with such focal vascular lesions under the heading of "focal cerebral infarction." In such cases, in the absence of a postmortem examination, it is not always possible to be sure that an actual thrombosis exists, for, as sometimes happens in the

case of the coronary arteries, cerebral infarction may occur owing to atheromatous changes in a vessel without the formation of an actual thrombus. The number of cases of cerebral hemorrhage is rather surprisingly small. It is my impression that cerebral hemorrhage has grown on the whole less frequent, but the change may be more apparent than real, and may be due to the fact that we have come to recognize that in many cases what we should previously have called cerebral hemorrhage is in fact an example of cerebral infarction.

Hypertension was present in approximately 50% of the 200 patients.

Table 2 illustrates the relative frequency of the principal presenting symptoms in the 200 patients. Subarachnoid hemorrhage is not, strictly speaking, a symptom, but it is a convenient shorthand for the group of symptoms to which it gives rise. It occurred in 15% of cases. Hemiplegia or monoplegia was slightly less frequent as a presenting symptom. Epilepsy of late onset was in this series due either to cerebral arteriosclerosis or to

TABLE 2

Cerebral Vascular Disease

200 Cases

Principal Symptoms

Subarachnoid Hemorrhage	30
Hemiplegia or Monoplegia	28
Epilepsy	18
Dementia	9
Parkinsonism	8
Aphasia	6
Hemianopsia	6
Pseudobulbar Palsy	3
Involuntary Movements	3
Thalamic Hemiplegia	2
Minor Episodes	87

cerebral angioma. Dementia did not occur very frequently as the presenting symptom; the reverse, of course, would be the case in a series taken from a mental hospital. Parkinsonism is also a relatively infrequent symptom of cerebral arterial disease, since most patients suffering from Parkinsonism owe their disorder either to encephalitis lethargica or to the degenerative disorder, idiopathic Parkinsonism, which appears to be unrelated to disorders of the cerebral circulation. Most of the other categories call for no special comment. Of the three patients with involuntary movements, one suffered from hemiballism, one from chorea and one from tremor. Eighty-seven patients suffered from minor, and often transitory, cerebral episodes which did not fall into any of the above clear-cut categories.

THROMBOSIS OF THE INTERNAL CAROTID ARTERY

One important advance in our knowledge of cerebral vascular disorders, which we owe largely to angiography, has been the recognition of the symp-

toms produced by atheroma or thrombosis of the internal carotid artery. The effects of partial or complete obstruction of this vessel are complex, since they depend on the adequacy of the collateral circulation through the circle of Willis, and also upon whether clots form in the branches of the internal carotid artery, or possibly are carried to them as emboli from the main trunk.

Prodromal symptoms consist of transient attacks of amblyopia in the eye on the affected side and transient symptoms of impaired circulation through some part of the ipsilateral cerebral hemisphere. Such attacks may lead to sudden and brief loss of consciousness, periods of mental confusion, transient attacks of speech disturbance, of weakness of one limb or the opposite half of the body, of paresthesias or sensory loss, or of focal or even generalized epilepsy.

The effects of complete and permanent occlusion are extremely variable. There may be no symptoms at all if the collateral circulation through the circle of Willis is given time to provide an adequate supply to the hemisphere normally fed by the affected vessel, and if the other vessels are in a condition to meet this demand. At the other extreme, thrombosis of the internal carotid may cause massive infarction of the whole area of the hemisphere normally supplied by the vessel, leading to severe hemiplegia, hemianesthesia, hemianopsia and, when the left hemisphere is affected, also aphasia. Between these two extremes are those patients who are left with some persistent disability which seems more often to be motor than sensory. When one internal carotid artery has been occluded the whole circulation of the brain must depend upon the opposite internal carotid and the two vertebral arteries. If these also are atheromatous they may prove inadequate to the task, which may mean that ischemic episodes subsequently involve even the cerebral hemisphere supplied by the "normal" carotid.

Angiography

What I have already said well illustrates how much light angiography has thrown upon the diagnosis of cerebral vascular lesions. It is true that this procedure is not entirely devoid of risk, especially in patients suffering from cerebral atheroma. Mishaps, however, are rare, and would seem to be more than counterbalanced by the new diagnostic knowledge. One should not hesitate to use angiography if one suspects the presence of an angioma or an aneurysm, not even in the presence of cerebral vascular disease if it is necessary to exclude an intracranial tumor.

The Use Of Anticoagulants

Dr. Irving Wright has demonstrated the value of anticoagulants in the prevention of cerebral embolism and has drawn attention to the problems inherent in their use in cases of suspected cerebral thrombosis. Not only

is it necessary first to be sure that the disorder is a thrombosis and not a hemorrhage, but there may also be some risk that hemorrhage may occur from the area of infarction produced by a thrombosis if the coagulability of the blood is lowered. No doubt for these reasons, there has been very little use of anticoagulants in the treatment of cerebral vascular lesions in England, but as we learn more about the disturbances of functions resulting from arteriosclerosis of the internal carotid artery we should be better able to assess the indications for their use in the prevention of thrombosis of this vessel and its branches.

CEREBRAL VASCULAR DISEASES: THEIR SIGNIFICANCE, DIAGNOSIS AND PRESENT TREATMENT, INCLUDING THE SELECTIVE USE OF ANTICOAGULANT SUBSTANCES*†

By Irving S. Wright, M.D., F.A.C.P., and Ellen McDevitt, M.D.,
New York, N. Y.

Cerebral vascular diseases include some of the most serious and widespread of disease processes which still remain among those most neglected. They have been treated too long with a fatalistic philosophy rather than a dynamic one, and no serious attack has been made on the social, economic and personal problems they present.

A conference dealing with many aspects of cerebral vascular diseases was recently held in Princeton under the auspices of the American Heart Association and the National Heart Institute, and acknowledgment is herewith made to the participants in the conference for many of the comments contained in this brief presentation.

The true dimensions of this problem are still obscured by lack of knowledge of the various diseases involved, by inadequate and incorrect diagnoses, and by sparse statistical data. Even the best available statistics cannot be looked upon as completely satisfactory or definitive. However, they do present the problem in its broad outlines. They are here presented in round numbers.‡

In 1952 *170,000* people died in the United States of cerebral accidents—or strokes. This is over *three* times the number who died from diabetes and tuberculosis combined in the same year.

It is estimated that there are *1,800,000* victims of cerebral vascular diseases in the United States today. When it is realized that a large but unknown percentage of these require from *one* to *four* people to care for them, the impact on community and family life becomes more apparent.

Cerebral arteriosclerosis is the second leading cause of first admissions to the state mental hospitals, schizophrenia being the leading cause. If first admissions listed under senility are included with cerebral arteriosclerosis, these causes combined account for 25% of all first admissions to state mental hospitals. This has been a continuing upward curve over the years. In 1950 *60,000* such patients were in state hospitals; this does not

* Presented as a Morning Lecture before the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

From the Department of Medicine of the Cornell University Medical College and the New York Hospital.

Aided by grants from the Kress, Lasker, Hyde and Hampill Foundations, and the U. S. Public Health Service.

† By special arrangement this paper will appear simultaneously in *The Lancet*.

‡ Acknowledgment is herewith made to the Albert and Mary Lasker Foundation for aid in compilation of the statistics quoted here.

include similar patients in county, city, Veterans Administration or private hospitals, or those cared for at home. *Seventy-three per cent* of all deaths caused by cerebral vascular diseases in 1952 occurred in people *65* years of age or older. Looking at this in the reverse, *27%* occurred in the highly productive years *under 65*.

Forty-four thousand deaths from cerebral vascular diseases in 1952 were in the "working age" group of 25 to 64 years. Many patients, especially those with rheumatic heart disease, suffer their first cerebral accident in early adulthood and remain incapacitated for years thereafter.

From the viewpoint of national economy, if these *44,000* people had lived even a single additional healthy year they could have earned on an average of over $151,000,000 and would have paid the Federal Government *$18,500,000* in taxes. The average per capita cost per year per patient in a state mental hospital is $777. This really represents very minimal care in many states, but on this basis the cost for the *60,000* cerebral vascular diseases patients in these hospitals is *$46,500,000* a year.

These are the cold statistics of a National and community problem, but what of the individual and his or her family? Here the tragedy strikes home. We all know of the middle aged man who is earning a good living and is a respected member in his community. He has *three* children in school. They have the things Americans have come to expect from life. Suddenly he suffers a cerebral accident and is paralyzed. No longer a self-supporting and self-sufficient member of society, he loses his income and requires nurses, doctors and probably hospitalization for an indeterminate time. While he may make a satisfactory recovery, if he does *not* the family economy is rapidly depleted, someone must remain in constant attendance, the education of the children is interrupted, the social status of the family deteriorates, emotional and maladjustment problems arise, the patient changes from a happy, well balanced person to an embittered, belligerent, difficult person—and from being a taxpayer he probably becomes dependent on his community.

This is a common picture—too common and too tragic.

Diagnosis: Until recently the diagnosis was an academic matter from the viewpoint of clinical medicine. Today it is increasingly important to determine whether neurologic signs of an intracranial lesion are due to hemorrhage, local thrombosis, embolism from a fibrillating heart, aneurysm of a cerebral artery, or a tumor. If the type of lesion and its location are fortunate, some form of therapy can now be at least logically considered for many patients. This discussion is concerned with the first three of these possibilities. A few general statements which may prove helpful in formulating a diagnosis are summarized as follows:

Given patients with a normal blood pressure, between 60 and 85% of deaths due to cerebral vascular diseases are probably related to thrombosis, provided the cardiac rhythm is regular. Hemorrhage and embolism make

up the residual percentages. These figures are based on autopsy findings but these vary widely in different series. The incidence of recovery from thrombosis, as determined by evidence of previous thrombi seen at autopsy, is high. In clinical practice the actual incidence may be in even greater proportion to the total number of clinically diagnosed cerebral episodes.

If the heart rhythm is irregular, especially in the presence of auricular fibrillation, the incidence of cerebral embolism increases relatively and thrombosis becomes correspondingly less common. This is especially true in those patients with old rheumatic heart disease under the age of 55.

When the blood pressure is elevated the incidence of hemorrhage increases and thrombosis assumes a relatively lesser rôle, although it continues to dominate according to most studies.

The history of previous thrombotic episodes or the presence of other evidence of generalized arteriosclerosis with occlusive phenomena is associated with a greater likelihood of cerebral thrombosis.

Evidence of increased intracranial pressure, such as choked discs, unequal pupils, a feeling of marked fullness with headache, increased manometric readings, or signs of rapidly spreading neurologic involvement, suggests space-occupying lesions such as hemorrhage, with or without tumor.

The acquisition of useful knowledge regarding the appearance and pressure of the spinal fluid has been hindered by the hesitancy of many clinicians, even some neurologists, to perform the simple procedure of the spinal puncture. This is largely based on a fear that death may ensue due to a sudden shift in pressure with a compression of the brain stem into the spinal canal. With proper technic and reasonable caution this risk is reduced to an insignificant level, and 5 c.c. or so of fluid removed slowly may greatly clarify the diagnosis. If the tap has been done cleanly, bloody or xanthochromic fluid indicates hemorrhage and contraindicates any serious consideration of anticoagulant therapy. Clear fluid does not completely rule out hemorrhage within the brain substance, but in connection with other factors, such as those mentioned above, may lay a fairly sound basis for the diagnosis of thrombosis or embolism, in which case anticoagulant therapy may be considered.

Electroencephalographic studies may be entirely normal in the presence of rather important lesions of the brain, including vascular lesions. However, if the first tracings after a "stroke" show definite abnormalities compatible with this type of lesion, and if these show progressive changes suggesting improvement during the subsequent weeks, this favors a vascular accident rather than a brain tumor. Electroencephalography is not, however, to be regarded as an infallible diagnostic procedure in differentiating these conditions.

While angiography has frequently proved helpful in the diagnosis and location of aneurysms and some types of tumors, it is of little or no value in the study of hemorrhage, thrombosis or embolism, and it is not without risk.

Vasospastic Phenomena: There is increasingly strong evidence that vasospasm can occur in the cerebral vessels just as it does elsewhere in the vascular tree. We see many patients who have a series of transient or "little" strokes which may range in severity from slight numbness or weakness of the side of the face, or slight difficulty with speech, to hemiplegia, and which may last for from a few minutes to several days, with complete recovery. They may recur repeatedly in the same day. Some of these may be due to minute thrombi, but many, probably a majority, are based on temporary spasm of the arteries involved. These phenomena have been too casually regarded in the past. They frequently presage a major paralysis, with all of its potential tragedy. The frequency with which such reactions are immediately preceded by intense emotional strain or disturbance suggests that in some instances there is a direct relationship, but in other instances no such relationship can be established. Treatment has the best chance of being effective in these cases if undertaken promptly.

Treatment of Cerebral Vascular Diseases: Any suggestions regarding present day treatment must be qualified by the acknowledgment that in all probability the discovery of a method to prevent or reverse the development of atherosclerosis will eliminate or greatly delay the onset of most of the effects from cerebral vascular diseases. While such a discovery may appear to some observers to be "just around the corner," the history of science is replete with discoveries which have remained frustratingly aloof for many years beyond the schedules of optimistic investigators. Therefore, pending actual accomplishment of the fact, we must devote attention to the problems at hand—the treatment of the phenomena presently encountered.

The Treatment of Cerebral Hemorrhage: The location of the hemorrhage is of the utmost importance. Today surgery should be seriously considered for the relief of the pressure of subdural or extradural hemorrhages. Patients frequently regain power and even consciousness promptly upon the removal of such pools of blood or clots. These hemorrhages most frequently occur following severe trauma to the head, and this history is helpful in establishment of the diagnosis. The surgery should be performed promptly, and preferably with the blood pressure markedly reduced.

The more common spontaneous cerebral hemorrhage does not as yet lend itself to specific therapy. The patient should be kept at complete rest, and if his blood pressure is markedly elevated efforts should be made to reduce it by phlebotomies or by the use of the various hypotensive drugs. Continuous intravenous infusion of sodium nitroprusside solution has been used for very acute cases.

Massive hemorrhage within or without the brain tissue frequently results in death, but autopsy studies suggest that many small hemorrhages may occur without death of the patient—in fact, in some instances without his knowledge of serious trouble.

Treatment of Thrombosis: In many places the conventional form of therapy for cerebral thrombosis is still largely expectant on the part of pa-

tients and physicians as well. The patient is placed at rest and the so-called vasodilator drugs administered. The evidence that they increase blood flow to the brain or aid the situation in any way is decidedly inconclusive, the possible exception being parenteral papaverine. When sedatives are necessary to assure rest, the barbiturates, known to be depressors of many critical brain centers, are often used in too large doses.

If the blood pressure is markedly elevated, let us say to a range of 190/110 or higher for either the systolic or diastolic, consideration should be given to reducing it, but not very rapidly, since that may encourage stagnation in the area of the thrombosis, with increased tendency to propagation of the clot.

The work of Kety and others [1] demonstrated that increased CO_2 in the blood does increase the blood flow to the brain. The inhalation of this would therefore appear to be a sound therapeutic approach. We do not know for certain, however, that the mere passage of more blood through the vascular tree is necessarily beneficial if that blood is laden with increased amounts of CO_2. It is generally assumed that it is beneficial, regardless of this question, but final proof is wanting at present.

The use of the stellate ganglion block has been advocated during recent years. Favorable reports suggest striking improvement during the early days following a cerebral thrombosis. It is essential to bear in mind the natural course of this syndrome and the fact that many, if not most, of these patients show striking improvement during the first week or 10 days. No significant increase in cerebral blood flow is produced by this procedure. Some patients have shown remarkable improvement coincident with the block, only to relapse shortly thereafter. The second and third blocks may or may not be accompanied by permanent improvement. Final evaluation of the indications and usefulness of this procedure must await more extensive experience.

The use of anticoagulant drugs in the treatment of cerebral thrombosis has been under study since our preliminary report in 1946.[2] This seems logical as an endeavor to (a) prevent propagation of the original thrombus which might occlude additional branches of the involved artery, thus increasing the size of the infarcted area; (b) prevent the development of additional thrombi in other vessels, a not uncommon occurrence in the brain; (c) encourage the more rapid disintegration of the original thrombus by the enzyme systems in the blood, which may have a freer action in the presence of adequate anticoagulant therapy.

Risks which must be evaluated include (a) an erroneous diagnosis of thrombosis or embolus, when the condition is actually hemorrhage which may be aggravated by anticoagulants; (b) the aggravation of hemorrhage in the cerebral infarct; hemorrhage is frequently encountered in all infarcts but this type of hemorrhage is rarely if ever aggravated by anticoagulant therapy when it occurs in other tissues such as the heart, lungs or kidneys. However, less is known about the behavior of hemorrhage in brain infarcts

during anticoagulant administration; (c) hemorrhage elsewhere in the body, a calculated and well understood risk inherent in all anticoagulant therapy. Our results with anticoagulant therapy in the treatment of both thrombosis and embolism will be summarized later in this paper.

In the treatment of embolism several additional factors must be considered. Since most cerebral emboli arise from mural thrombi in the heart, secondary either to old rheumatic heart disease with auricular fibrillation or to myocardial infarction, the primary cardiac problem requires serious attention. Decompensation should be actively treated. The existence of the original thrombus constitutes an additional indication for anticoagulant therapy. The patient may survive the first embolus only to succumb to succeeding ones arising from the same source unless the tendency to propagation is successfully interrupted.

Recently a new aspect of this phenomenon has been encountered which requires additional study and thought. There have been a number (although the total is unknown) of cerebral emboli as well as emboli to other sites in the body which have occurred at the time of surgery for mitral commissurotomy. We have seen nine such cases in the past year. This may result in hemiplegia or other serious complications, as in a recent case with multiple emboli producing aphasia with simultaneous gangrene and loss of a foot. The embolism usually results from the breaking up of a friable and actively propagating thrombus within the left atrium. Pathologic studies have shown that mural thrombi in the hearts of patients treated for 10 days or more with anticoagulants tend to be more smoothly sealed over with a fibrin coating, and with fewer friable and irregular fibrillating tails. It appears logical, therefore, to place patients on anticoagulants for from 10 to 30 days in preparation for a commissurotomy, despite the present lack of statistical proof of its value. Because of the relative rarity of these complications, such proof may not be forthcoming for some time.

Further Experience with the Treatment of Cerebral Thrombo-embolism with Anticoagulants: In 1946 [3] and 1947 [4] we reported preliminary experience with the use of Dicumarol in the treatment of patients with rheumatic heart disease with auricular fibrillation and multiple emboli. Since then others have confirmed our observations,[7, 8] and recently we have analyzed the course of 57 patients who have suffered from cerebral thrombo-embolic episodes and have thereafter been treated with anticoagulants.[12] The series with rheumatic heart disease now consists of 31 patients, 29 of whose hearts were in fibrillation. There were 19 with cerebral thrombosis on the probable basis of arteriosclerosis of the cerebral vessels or with cerebral embolism resulting from coronary arteriosclerosis with myocardial infarction, seven patients were included with a variety of diagnoses in whom cerebral thrombo-embolic complications had occurred.

Table 1 shows that in the period of 463 months and 19 days after their first thromboembolic episode and before anticoagulant therapy the 31 patients with rheumatic heart disease experienced 137 embolic episodes, 46

TABLE 1

THROMBOEMBOLIC EPISODES IN 31 PATIENTS WITH RHEUMATIC HEART DISEASE

NUMBER OF PATIENTS	TOTAL PATIENT MONTHS	TOTAL THROMBO-EMBOLIC EPISODES	CEREBRAL VASCULAR
BEFORE ANTICOAGULANT THERAPY			
31	463 MONTHS 19 DAYS	137	46
DURING ANTICOAGULANT THERAPY			
31	709 MONTHS 22 DAYS	11	4

of which were cerebral in location. After anticoagulant therapy was started, during a total period of 709 months and 22 days (a much longer period), this same group of patients experienced only 11 embolic episodes, four of which were cerebral.

Only one embolic episode occurred when the prothrombin time was within the range considered to produce optimal anticoagulant protection, namely 20 to 40 seconds (control time, 15 seconds ± 1).

One group of *six* patients with rheumatic heart disease and auricular fibrillation who remained on anticoagulants continuously for 162 months suffered no thrombo-embolic episodes. This was in contrast to 16 episodes within 45 months prior to anticoagulant treatment.

TABLE 2

THROMBOEMBOLIC EPISODES IN PATIENTS WITH RHEUMATIC HEART DISEASE DURING INTERMITTENT ANTICOAGULANT THERAPY

CASE NUMBER	EMBOLI BEFORE ANTICOAGULANT THERAPY	PATIENT MONTHS EMBOLI OCCURRED	INITIAL PERIOD OF TREATMENT MONTHS	INITIAL PERIOD OF TREATMENT DAYS	INTERRUPTION MONTHS	INTERRUPTION DAYS	EMBOLI	FURTHER PERIODS OF TREATMENT MONTHS	FURTHER PERIODS OF TREATMENT DAYS	EMBOLI
3	4	36	42			9	2	30		1-DEATH
4*	4	9	14		1	3	1	43		0
12	3	15 DAYS		2		20	1		12	DEATH
27	5	24	3	20		27	2-DEATH			
28	4	21	7			14	1	17		0
31	1		5	13	2		1	13		0
34	3	3	10			7	2	3		0
43	20	132	42		1		1	42		2 ?
44	17	58	1	13	1 1	25 10 7	2 1		15 6	 DEATH
47*	2	2		16		8			2	DEATH
50	1		3		2		0	69		0
55	4	48	3			7	0	87		0

* CARDIAC SURGERY PERFORMED DURING INTERRUPTION

When anticoagulant therapy was interrupted, serious thrombo-embolic complications occurred in 10 of 12 patients with rheumatic heart disease in whom therapy was not continuous (table 2). Five of this group died, and in four instances death was directly related to thrombo-embolic complications arising during the period of interruption of anticoagulant therapy. The following examples are illustrative of our experience with this group of patients.

Further examples of this nature are summarized in table 2.

Case Reports

Patient 3 was a 53 year old white female with rheumatic heart disease who developed auricular fibrillation and one year later had a transient period of left hemiparesis. Two years later she had a myocardial infarct and two months later an embolus to the right popliteal artery. Anticoagulants were begun at this time and continued for 42 months without further embolic episodes until it became necessary, it was thought, to reduce her anticoagulant level to allow for the extraction of a tooth. There was an unforeseen delay in extraction and the patient remained off anticoagulants for nine days. Anticoagulants were started again the day of extraction, but before there was a sufficient protection, and at a prothrombin time of 18.2, she had a transient left hemiparesis and also an embolus to the right brachial artery. These both cleared rapidly. Anticoagulants were continued and she remained in her usual state, able to do light housework and make weekly visits to the anticoagulant clinic, until September 9, 1953, almost six years to the day of her being placed on anticoagulants, when she was admitted to another hospital service with evidence of left cerebral damage. The prothrombin time on admission was 19.4. The patient remained in a comatose state during the 10 days of hospitalization. She received depo-heparin; however, no clotting times were reported. The prothrombin time did not exceed 23 seconds. At autopsy there was evidence of two anemic infarcts on the right, and in the left internal capsule there was a large hemorrhagic infarct. Whether the final episode was hemorrhagic or embolic is difficult to say. It is conceivable that embolization occurred and that with the prolongation of clotting time by heparin excessive bleeding ensued.

Patient 4, a 41 year old white male artist, was admitted to New York Hospital for evaluation before valvulotomy. He had previously experienced four arterial emboli and had been maintained on anticoagulants for a period of 14 months without embolization. Anticoagulants were discontinued one month and three days prior to the operation, a period we now consider too long. At the time of operation a thrombus was found in the auricular appendage which was not flushed out, as is now done routinely. When the patient recovered from the anesthesia it was found that he had a right hemiparesis. He was immediately restarted on anticoagulants and has had no further embolization in the subsequent 43 months to date.

In some individuals embolization may occur in rapid succession, and patient 43 is an example.

Patient 43. This patient had experienced a total of 20 emboli, nine occurring in the 10 days before anticoagulants were instituted on December 6, 1946. She remained on anticoagulants for 42 months and at that time decided to forego this therapy. Thirty days later she had a saddle embolus which broke and lodged in the smaller vessels of both legs, without loss in tissue. Since this incident she has remained on anticoagulants. Except for one episode of transient dizziness and

numbness and coldness of the right hand, at a time when her prothrombin time was low, she has experienced no other complications.

Four of the six deaths occurred among those with rheumatic heart disease who were not given anticoagulants continuously.

Patient 44 was a 47 year old white female who developed auricular fibrillation in 1941 and experienced her first embolic episode that year. Over the next five years she experienced at least 14 clinically recognizable embolic phenomena. After rapidly occurring emboli to the brain and the mesenteric and the peripheral vessels, she developed a pulmonary infarct and anticoagulants were given. The patient remained on anticoagulants for 43 days, at which time she was discharged from the hospital on digitalis, Mercuhydrin and ammonium chloride. After 55 days without anticoagulants she was re-admitted to New York Hospital with pulmonary and mesenteric emboli. She was again treated with anticoagulants for 15 days and discharged without anticoagulants. At this time there were no facilities for the home care follow-up of patients, and anticoagulants could not be given on an ambulatory basis because of the patient's inability to make clinic visits. Forty days later the patient had another pulmonary infarction and was re-admitted. She received anticoagulants for six days, at which time the prothrombin time was 43.5 seconds. She coughed up clots of blood and anticoagulants were discontinued. Vitamin K was given intravenously on three different occasions because of severe hemoptysis. The patient received no more anticoagulant therapy and died April 14, 15 days after her twelfth admission. At postmortem examination there was an anemic infarct in the brain, and an old organized mural thrombus in the left atrium, and a cast of clotted blood was found to occlude the left main bronchus.

Another, patient 27, had clinically recognizable emboli, two of which were cerebral. He was given anticoagulants 22 days following an embolus to a renal artery, and because the prothrombin time had become elevated beyond a safe level he received vitamin K and anticoagulants were discontinued. They were not started again after the prothrombin time returned to a safe range. The patient died after a series of pulmonary emboli, which were confirmed post mortem; he had been without anticoagulants for 28 days.

A 30 year old white female, patient 12, had three embolic episodes, one pulmonary and one cerebral, occurring three days apart. After the cerebral embolus, heparin was begun. After 48 hours the spinal fluid was reëxamined and found to be xanthochromic. Anticoagulants were discontinued and 20 days later the patient had another severe pulmonary infarction. Anticoagulants were started again. The patient died 11 days later and at post mortem an anemic infarct was found in the brain and multiple emboli were found within the pulmonary arteries. The prothrombin time on the day of death was 24 seconds.

Further examples of this nature are summarized in table 2. Many of the patients in this group represent very early experience with the problems presented by patients with an almost overwhelming tendency to thromboembolic complications.

Nineteen patients who suffered from cerebral vascular accidents believed to be on the basis of embolization arising from a mural thrombus secondary to myocardial infarction,[8] or to thrombosis of cerebral arteries, were treated with anticoagulants. Eight of these patients suffered 13 myocardial infarctions preceding other thromboembolic episodes; some thromboembolic episodes did occur at therapeutic levels (table 3). Thirteen of the 19 pa-

TABLE 3

PROTHROMBIN TIMES (SECONDS) RELATED TO THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH GENERALIZED ARTERIOSCLEROSIS

	UNDER 19.9	20-24.9	25-39.9	OVER 40	#
RENAL INFARCT	1		1	0	(2)
PULMONARY INFARCT		1	1	0	
CEREBRAL THROMBOSIS		1	1	0	

NOT ON DRUG

tients were hypertensive. In 248 months and 13 days before anticoagulant therapy 48 thromboembolic episodes occurred, 25 of which were cerebral. During 287 patient months (a longer period) of anticoagulant therapy the same patients suffered only eight thromboembolic episodes, of which two were cerebral, as in the cases of old rheumatic heart disease—a striking reduction.

The distribution according to location of complications before and after anticoagulant therapy is shown in table 4. As in patients with rheumatic heart disease, there is a striking relationship between the recurrence of

TABLE 4

THROMBOEMBOLIC EPISODES IN 19 PATIENTS WITH GENERALIZED ARTERIOSCLEROSIS

	BEFORE ANTICOAGULANT THERAPY	AFTER ANTICOAGULANT THERAPY
CEREBRAL VASCULAR	25	2
MYOCARDIAL INFARCTION	13 (IN 8 PATIENTS)	0
RENAL INFARCT	2	4 (1)
PULMONARY	2	2
PERIPHERAL	6	0

thrombo-embolic incidents and the intermittent use of anticoagulants. There were seven patients in this group in whom anticoagulants were used intermittently, and in each instance interruption of therapy was followed by recurrence of thrombo-embolic complications. The following illustrate graphically these relationships.

Patient 9 is a 53 year old white male who at the age of 50 experienced his first myocardial infarction, which was mixed in type. He was admitted to New York Hospital and anticoagulants were begun July 20, 1950, effective levels being reached within 72 hours, but dropping below therapeutic levels on six occasions. The patient made a satisfactory recovery and was discharged after 30 days. Anticoagulants were

discontinued at that time. Seven months later the patient suddenly developed pain and coldness in the left lower extremity from the knee down; anticoagulants were not given. Eleven months after this episode he developed evidence of a left hemiparesis which was transient, the only residual being a left facial weakness. Eight months later the second myocardial infarction occurred in the posterior base, and the patient was again placed on anticoagulants, this time for 40 days. On discharge, anticoagulants were again discontinued and three months later he developed sudden coldness and pain in the entire right lower extremity; an embolus was removed from the right femoral artery and anticoagulants were re-instituted. The patient has remained under this therapy since that time (11 months, 20 days) without further incident.

RELATIONSHIP OF INTERMITTENT USE OF ANTICOAGULANTS
TO RECURRENT THROMBOEMBOLIC EPISODES
AS SHOWN BY PATIENT 9

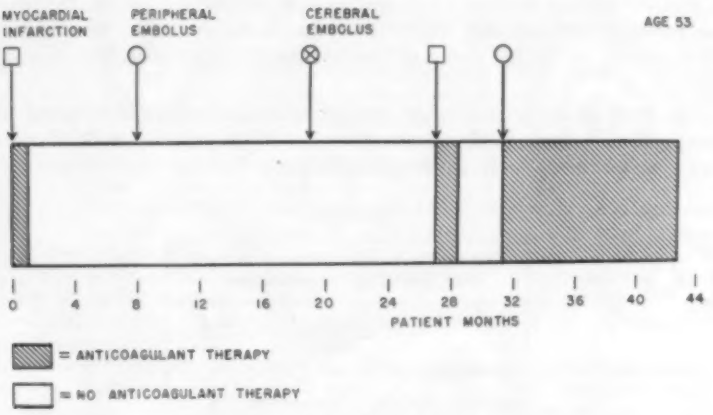

FIG. 1.

Patient 52, a 54 year old white female with known hypertension for 10 years, in 1950 had two myocardial infarcts requiring hospitalization, but no anticoagulants were given. In July, 1951, she was admitted to New York Hospital for anticoagulant therapy following embolization to a digital artery of the right third finger. Anticoagulants were employed, and she was discharged on anticoagulants, on which she continued for 46 days. Because of difficulty in traveling, the patient discontinued therapy. Seven months later she was re-admitted with another myocardial infarct and anticoagulants were resumed. She remained on anticoagulants until October 31, 1952, when she was readmitted because of severe epistaxis and evidence of a pulmonary infarction. Stool examinations at this time were guaiac positive. The prothrombin time was 35.5 seconds. Anticoagulants were discontinued. Ten days later she developed evidence of a left hemiparesis. During the three weeks preceding this admission three of the six determinations were below the therapeutic range and may have been a contributory factor in the pulmonary infarction which followed. The patient made a satisfactory recovery and was followed by the home care service

RELATIONSHIP OF INTERMITTENT USE OF ANTICOAGULANTS
TO RECURRENT THROMBOEMBOLIC EPISODES
AS SHOWN BY PATIENT 52

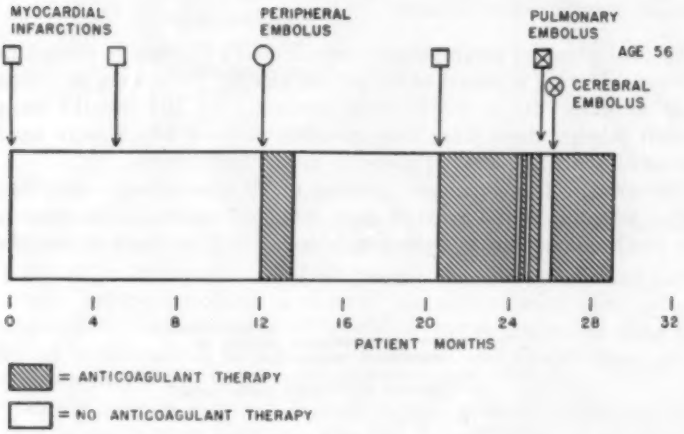

FIG. 2.

RELATIONSHIP OF INTERMITTENT USE OF ANTICOAGULANTS
TO RECURRENT THROMBOEMBOLIC EPISODES
AS SHOWN BY PATIENT 20

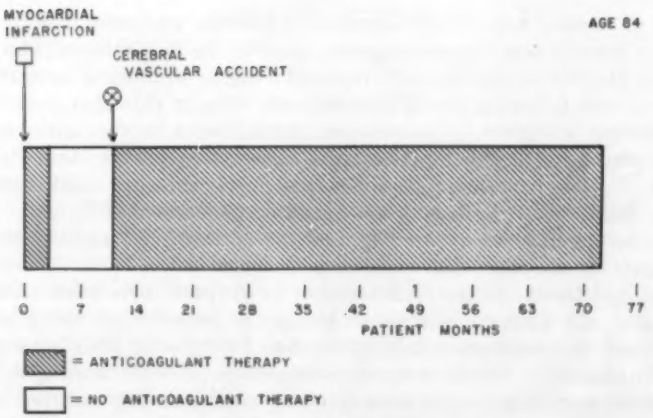

FIG. 3.

of New York Hospital for three months, remaining on anticoagulants during this period.

Patient 20 is an 84 year old white female who had a myocardial infarct in March, 1947. She was hospitalized for three months, receiving anticoagulants during that period. Eight months later she had a cerebral thrombosis and was again started on anticoagulants. She has now been on anticoagulants for 62 months, without further evidence of thrombo-embolic incident.

The final group of seven patients represented a number of miscellaneous diagnoses. During a period of 83 patient months there were 20 thrombo-embolic episodes, 10 of which were cerebral. In 165 months on anti-coagulant therapy there were four episodes, none of which were cerebral, and none of which occurred at adequate prothrombin levels.

Hemorrhagic Complications: A total of 29 hemorrhagic complications occurred in nine patients, most of them minor in nature. The relationship to the prothrombin time is shown in table 5. It is of interest that the in-

TABLE 5

PROTHROMBIN TIMES (SECONDS) RELATED TO HEMORRHAGIC COMPLICATIONS

	UNDER 19.9	20-24.9	25-39.9	OVER 40	UNKNOWN
HEMATURIA	1	1	1	4	
CEREBRAL HEMORRHAGE		1*		1	1*
EXCESSIVE MENSTRUAL FLOW			1		
MELENA			2	1	
EPISTAXIS			1		
ECCHYMOSIS		1	3	1	2
HEMOPTYSIS		1	3*	1	

* HEPARIN ◦ ASSOCIATED WITH PULMONARY INFARCTION

stances of cerebral hemorrhage occurred in patients who were hypertensive, and that heparin was the anticoagulant used in the two patients who died. Recently MacMillan and Brown [10] reported a higher instance of hemorrhagic manifestations following use of intramuscular heparin than that experienced when heparin was given by intravenous route or when another anticoagulant was employed. The other patient who experienced intracerebral bleeding made a complete recovery. There was one instance of increased menstrual flow in this group. Following a diagnostic dilatation and curettage there was no further episode of bleeding, and the patient has remained on anti-coagulants for six years with no further complications.

Cause of Death: In the total series of 57 patients there were 13 deaths (table 6). Of these, two occurred because of hemorrhagic complications as has been discussed previously (the causes of death in these patients are listed in table 6). Seven of these patients were still on anticoagulants at the time of death, the complication resulting fatally, having occurred during a period when anticoagulant levels were inadequate. Four patients were

TABLE 6

CAUSE OF DEATH		
	CEREBRAL VASCULAR DISEASE	RHEUMATIC HEART DISEASE WITH EMBOLIZATION
CONGESTIVE HEART FAILURE	4	
CEREBRAL HEMORRHAGE	1	1
CEREBRAL EMBOLI		1
CEREBRAL THROMBOSIS	1	
FRACTURED HIP	1	
POSTVALVULOTOMY VENTRICULAR TACHYCARDIA		1
PULMONARY EMBOLI		3

under adequate anticoagulant therapy at the time of death, the immediate cause of death, however, being unrelated to such therapy.

It should be remembered that all patients in this series were patients with severe heart disease and/or vascular disease, suffering from recurrent thrombo-embolic complications. The risk of complications of many types is inherent in the natural history of such disease, and complications are not therefore necessarily due to anticoagulant therapy.[9]

From the experience gained in studying this group of patients it is evident that anticoagulants may be utilized in the treatment of patients who

TABLE 7

SUMMARY			
NUMBER OF PATIENTS	PATIENT MONTHS	TOTAL THROMBO-EMBOLIC EPISODES	CEREBRAL VASCULAR
BEFORE ANTICOAGULANT THERAPY			
57	795	205	81
DURING ANTICOAGULANT THERAPY			
57	1162	23	6

have had cerebral vascular accidents due to thrombo-embolic complications. The precautions in the use of these drugs have been adequately discussed in previous communications from our group and many others.

The number of thrombo-embolic episodes actually occurring exceeds those diagnosed clinically. This has been confirmed by the report of necropsy material made by the Committee on Anticoagulants of the American Heart Association.[11] These findings were further substantiated in a group of 98 patients coming to necropsy with diagnoses of cerebral hemorrhage, cerebral thrombosis and embolism during the years 1942 to 1952

on the Second Medical (Cornell) Division of Bellevue Hospital (table 7). Of the 46 patients with anemic infarcts due to either thrombosis or embolism, 23 (50%) exhibited evidence of 50 major thrombo-embolic complications other than those occurring in the brain. These included pulmonary emboli, myocardial infarction, occlusion of the inferior vena cava, femoral vein, renal artery and the lower abdominal aorta. In many instances the immediate cause of death was thought to be the thrombo-embolic complication.

Fifty-two of these patients had evidence of hemorrhagic involvement in the brain. In 17 of these there were, in addition, 23 major thrombo-embolic complications. From these observations it seems reasonable to assume that these episodes represent the manifestation of a severe disturbance in the clotting mechanism, which may result in hemorrhage of clotting or even both simultaneously, and which is strongly influenced by

TABLE 8

MAJOR THROMBOEMBOLIC EPISODES IN 98 PATIENTS WITH CEREBRAL VASCULAR DISEASES AUTOPSIED AT BELLEVUE HOSPITAL, 1942 - 1952

TOTAL NUMBER OF PATIENTS	DIAGNOSIS	PATIENTS WITH COMPLICATIONS	NUMBER OF MAJOR THROMBOEMBOLIC COMPLICATIONS
46	CEREBRAL THROMBOSIS OR EMBOLISM	23	50
52	CEREBRAL HEMORRHAGE	17	23

local factors affecting the endothelial lining of the vascular system. These factors are as yet incompletely understood.

Value of Anticoagulants in the Treatment of Cerebral Vascular Accidents: It is difficult or impossible to obtain *conclusive* evidence which indicates that the use of anticoagulants has influenced the immediate course of a specific patient after a cerebral vascular accident has occurred.[12] It is, however, the impression of numerous observers that a favorable influence has been exerted. To accumulate additional evidence regarding this point a comparable group of control and treated patients must be studied; such a study is now in progress.

SUMMARY

1. Cerebral vascular diseases are among the most serious and common diseases.

2. The present state of knowledge of these diseases and the present results of treatment are far from satisfactory.

3. Differential diagnosis is no longer of purely academic interest, and various methods to aid in diagnosis have been discussed and evaluated.

4. Vasospasm occurs in the cerebral arteries and is of importance in terms of warning of more serious phenomena to come, and also because treatment may be of some help in preventing the serious sequences.

5. Cerebral hemorrhage is always serious. Surgical methods may be seriously considered for some subdural or extradural hemorrhages. Most other cerebral hemorrhages are not amenable to specific therapy at this time.

6. The use of sympathetic blocks for acute thromboses or emboli is under study at present; final evaluation remains for the future.

7. The use of anticoagulant drugs for the treatment of thrombosis and embolism is also in the process of investigation. Their trial appears justified, but future experience is essential for final evaluation.

8. Experience with the use of anticoagulants in the reduction of thrombo-embolic episodes in 57 patients treated for a total period of 1,162 months is summarized.

9. Fifty-seven patients during a period of 795 patient months before beginning anticoagulant therapy experienced 205 thrombo-embolic episodes, 81 of which were cerebral in location. Following institution of anticoagulant therapy, during a period of 1,162 patient months, these patients experienced 23 thromboembolic episodes, six of which were cerebral in location.

10. The reduction appears to occur in emboli arising from thrombi in the hearts of patients suffering from rheumatic heart disease or from acute myocardial infarction.

11. A reduction in the incidence of recurrent thromboses in the arteries of the brain has also been noted.

12. The risk from hemorrhage in the treatment of these diseases with anticoagulants is present but not excessive.

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PHYSIOLOGIC BASIS FOR THE CLINICAL USE OF NORADRENALIN *

By U. S. von Euler, F.A.C.P. (Hon.), M.D., *Stockholm, Sweden*

The therapeutic use of noradrenalin was suggested by Biberfeld [3] in Austria half a century ago because of its strong vasoconstrictor action and low toxicity, but his plea for the new drug evoked no response, and interest in noradrenalin as a drug was almost negligible before the late forties. Since that time the number of investigations dealing with its therapeutic applications has grown rapidly.

Probably the most valuable and informative basis for the rational use of noradrenalin is its function as sympathetic nerve transmitter and suprarenal medullary hormone.[5, 6, 16] Incidentally, the old claim that the so-called natural adrenalin from suprarenal extracts was superior to the synthetic compound may have been due to the admixture of some 20 to 30 per cent noradrenalin in the natural product.

Although the activities of noradrenalin in the body are as manifold as the functions of the adrenergic nerve system, chiefly the circulatory actions will be considered for the present purpose.

The evidence that noradrenalin serves as the adrenergic nerve transmitter is by now thoroughly established. Thus noradrenalin is present in all adrenergic nerves and in organs supplied with such nerves, notably in the spleen, heart and blood vessels. The nerve-free placenta lacks noradrenalin (figure 1).

Small amounts of adrenalin are found in extracts of nerves and tissues also, but there is so far no evidence that adrenalin is produced by adrenergic nerves. The adrenalin may well be derived from chromaffin cells present in the organs. This assumption is supported by the fact that after adrenergic nerve degeneration the noradrenalin disappears or is reduced to a higher degree than the adrenalin. On regeneration of the adrenergic nerves noradrenalin reappears.[14] In its rôle as mediator of vasomotor action noradrenalin is the primary regulator of the blood pressure, and its action on the vascular system and the heart determines the efficiency of the blood pressure homeostatic mechanism. We do not know whether a generalized reflex vasomotor action is identical in its action pattern with that of an intravenous infusion of the drug, but there are reasons to believe that the differences, if present, are not very large. After the release at the adrenergic nerve endings most of the noradrenalin is locally destroyed, probably partly by amine oxidase, but some escapes into the blood stream and is excreted through the urine.

* Presented as the Lilly Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

The general circulatory actions of the drug have been largely elucidated by the studies of Goldenberg and his co-workers in 1948.[18] By using continuous infusions in man they found that doses from 0.05 μg. per kilogram per minute and higher raise both the systolic and the diastolic blood pressure. Since the cardiac output does not change, this means an increased peripheral resistance due to vasoconstriction. The heart frequency in man is reduced as a result of reflex vagal action, which conceals the positive chronotropic effect. This reflex, which is elicited by the stretch receptors of the carotid sinus and aorta, is abolished by atropine. Noradrenalin also exerts a strong positive inotropic effect. The coronary vessels are dilated, allowing an increased blood flow to the heart muscle.

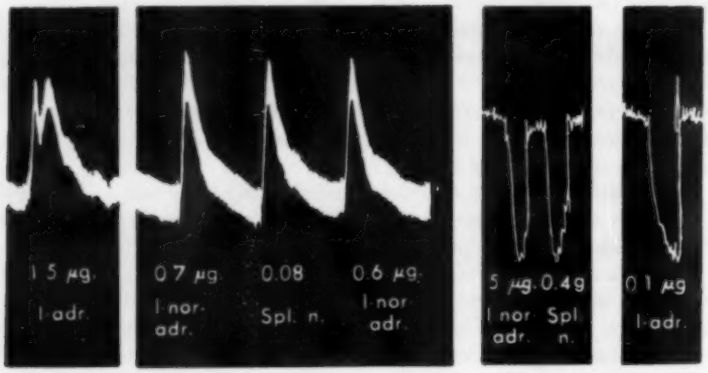

FIG. 1. Blood pressure, cat. Effect of 1.5 μg. adrenalin, 0.7 μg. noradrenalin, 0.08 gm. extract of splenic nerves (cow), 0.6 μg. noradrenalin. Fowl's rectal cecum. Effect of 5 μg. noradrenalin 0.4 gm. splenic nerves and 0.1 μg. adrenalin. (From Thudichum Memorial Volume, by courtesy of Charles C Thomas, Publisher.)

The actions of noradrenalin are different from those caused by adrenalin, which in moderate amounts in man causes vasodilatation as a net effect. Adrenalin does not raise the diastolic pressure to the same extent as the systolic pressure. The mean effective pressure thus may be considerably lower with adrenalin than with noradrenalin, even when the systolic pressure is the same.

Both adrenalin and noradrenalin constrict the cutaneous and part of the splanchnic vessels, but they differ markly as regards the muscle blood flow. This is usually decreased by noradrenalin but considerably increased by adrenalin.[1]

The blood vessels to the liver,[2] the kidney [27] and the brain [28] are constricted by moderate doses of noradrenalin, but usually this effect is nearly compensated for by the increased pressure head.

The redistribution of the blood in the body during infusion of moderate doses of noradrenalin thus seems to be relatively moderate, and in most

organs of greater importance the flow is not impaired in spite of the vasoconstriction. This is what should be expected if noradrenalin is the primary regulator of the blood pressure level. With adrenalin, on the other hand, vasodilatation occurs not only in the heart but also in skeletal muscle and in the liver, and in spite of an increased total output of the heart the effective mean pressure head is lower. Since the vasoconstriction may be as intense in some organs as with noradrenalin, the flow in these organs will consequently be reduced. This is the case in the skin, where it is of little concern, but it may also occur in the kidney.

Direct measurements of the venous return in open-chest anesthetized dogs subjected to various procedures causing a change in the peripheral resistance, including administration of noradrenalin, have shown that the venous return changed in the same direction as the peripheral resistance.[22] The effect is interpreted as a result of active changes in the post arteriolar blood vessels, most likely the veins.

TABLE 1

Effect of Adrenalin and Noradrenalin on Various Vascular Regions

	Adrenalin	Noradrenalin
Skin Vessels	Constr.	Constr.
Kidney Vessels	Constr.	Constr.
Brain Vessels	(Constr.)	(Constr.)
Lung Vessels	(Constr.)	(Constr.)
Muscle Vessels	Dil.	(Constr.)
Liver Vessels	Dil.	Constr.
Heart Vessels	(Dil.)	Dil.

Brackets denote weak or inconsistent action.

Table 1 shows the effect of noradrenalin and adrenalin on various vascular regions.

The fact that the pulmonary, the muscular and the cerebral vessels are relatively insensitive to noradrenalin apparently has a counterpart in their sparse vasomotor supply. This is also in keeping with the fact that the lungs, striated muscle and the brain normally contain little noradrenalin in comparison with other organs, such as the spleen, the kidneys, the salivary glands and the heart. Thus the lungs and brain contain only about 1/10–1/20 of the noradrenalin in the spleen.

It is thus apparent that the circulatory actions of noradrenalin differ in important respects from those of adrenalin. Apart from the circulatory actions, noradrenalin also differs significantly from adrenalin in some other respects. Thus the metabolic actions of adrenalin, as, for example, on total oxygen consumption, blood sugar, blood lactic acid, number of white blood cells and so forth, occur to only a small extent with noradrenalin. To obtain the same actions as with adrenalin, about five to ten times higher doses of noradrenalin are required. This has an important bearing on the question of the so-called wasteful O_2 consumption of the heart. There is good

evidence that adrenalin causes an effect of this kind, but there is little reason to suspect that this effect occurs with noradrenalin to any appreciable extent. For the therapeutic use in cases with diseased hearts this effect of adrenalin is clearly of high significance. On the other hand, it would be awkward if the organism used a tool in the blood pressure homeostatic mechanism which caused untoward effects on the heart.

Another difference of interest is that the subjective symptoms in man after noradrenalin are much weaker than after adrenalin, probably due to the weak metabolic effects on nerve structures of noradrenalin.

The effect of a chronic infusion of large amounts of noradrenalin can be conveniently studied in certain cases of pheochromocytoma, where the amounts "infused" from the tumor may be as high as 1 to 2 μg. noradrenalin per kilogram per minute, or about 5 mg. per hour [7] (figure 2). From the

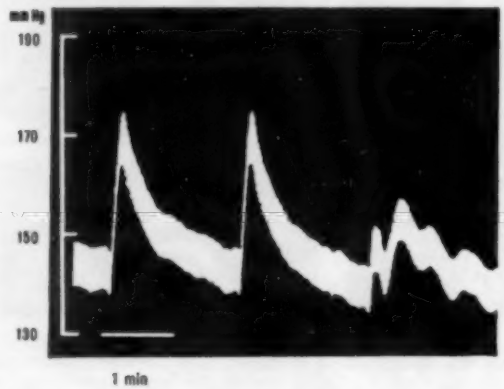

FIG. 2. Blood pressure, cat. Effect of injection of 0.1 ml. urine from a patient with pheochromocytoma, followed by 0.3 μg. noradrenalin and 0.4 μg. adrenalin.

information gained in such cases it can be concluded that chronic infusion of large doses does not lead to tachyphylaxis, the blood pressure remaining elevated as long as the tumor continues to release noradrenalin. The heart apparently suffers little damage from the continuous secretion, since it may work for years at the high pressure. Metabolic changes are usually mild, though sweating and muscular weakness may occur, probably as a result of sudden increases in the release. The subjective symptoms are as a rule not very pronounced. In fact, many cases may pass as essential hypertension, due to the unobtrusiveness of the symptoms.

If we can predict from the results of physiologic experiments and clinical experience when noradrenalin may be expected to be of therapeutic use, we may also be able to obtain information by observing the conditions under which noradrenalin is released from the nerves and the suprarenals.

The suprarenal glands of nearly all vertebrates contain noradrenalin,

though the proportion varies between a few per cent (whales) and nearly 100 per cent (rabbits) of the sum of adrenalin and noradrenalin. In a series of cases of adrenalectomy in man the fresh gland contained on an average 0.09 mg./gm. noradrenalin, corresponding to a total amount of 1 to 2 mg. It can be assumed that the noradrenalin is stored in the gland for emergency purposes, and it is of interest to note that the fetal organism has much noradrenalin in its store but very little adrenalin.[15]

It is known that the sympathetic vascular nerves are activated by deflation of the carotid sinus, as, for example, during carotid occlusion, or when the pressure drops in the aorta. Under such conditions the suprarenal glands also increase their secretion.

The release has been studied directly in experiments on cats in which the suprarenal blood has been collected and assayed. Analysis has revealed

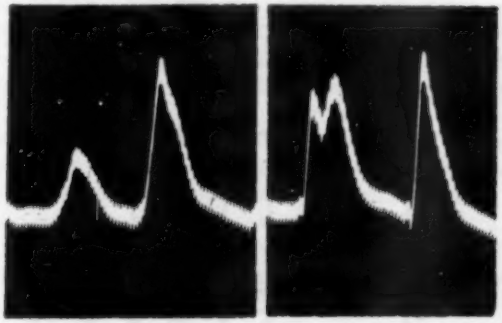

FIG. 3. Blood pressure, cat. Effects of injections of 1 ml. suprarenal venous blood from "spontaneous" secretion and during carotid artery occlusion, followed by 0.4 μg. adrenalin and 0.25 μg. noradrenalin. (From U. S. von Euler et al., Scandinav. J. Clin. and Lab. Invest. 5, 122, 1953.)

that about 75 per cent of the secretion consists of noradrenalin,[17] which is in contrast to the selective secretion of adrenalin during hypoglycemia,[4] or the high percentage of adrenalin during stressful stimuli [7] (figure 3).

Also by studying the excretion of noradrenalin in urine we may obtain information about the conditions under which it is released in the organism. Normally a small proportion of the noradrenalin produced in the body is excreted,[9] and it can be shown that this differs according to the state of activity and other factors. During night rest or in recumbent position the excretion is low but it increases during head-up position [26] or muscular work [10] (figure 4).

If the natural release of noradrenalin is prevented by ganglionic blocking agents, muscular work is accompanied by a profound fall in blood pressure.[24] It has also been shown that during postural hypotension in man the noradrenalin secretion is lower than normal.[20]

After adrenalectomy in man the adrenalin excretion is strongly reduced, while the noradrenalin excretion is unchanged or even increased.[8] Signs of circulatory insufficiency are not generally observed in patients adequately maintained on cortisone, which speaks against adrenalin's having a determinant rôle in the blood pressure homeostasis.

Since noradrenalin is the chief factor for the maintenance of the normal blood pressure and represents the emergency hormone used by the organism to raise a low pressure, it is not surprising that it should be tried in clinical situations of lowered arterial blood pressure with either unchanged or decreased flow. The use of noradrenalin in circulatory deficiency was initiated by Goldenberg et al.[12]

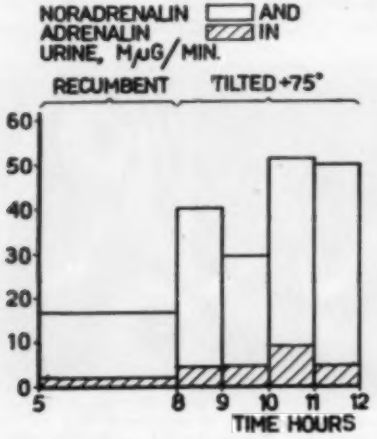

FIG. 4. Noradrenalin and adrenalin excretion in urine in normal individual during recumbent and head-up position (Sundin and Euler, 1954).

In the first condition the blood pressure homeostatic mechanism is probably functionally defective. This may be encountered in cases of lowered sympathetic tone caused, for example, by spinal anesthesia, sympathectomy, ganglionic blocking agents and drugs paralyzing the central vasomotor mechanism. Unless the blood pressure drops to low values, the condition is not serious because the flow remains adequate. On the other hand, certain functions will suffer if the pressure remains low for any length of time. In these conditions the pressure is usually readily restored with noradrenalin, which then actually serves as substitutional therapy. The rise in blood pressure is not accompanied by gross alterations in flow.

The second condition is more serious and more complex, and is encountered in certain states of shock. Noradrenalin was first used in cardiogenic shock by Kaindl and Lindner,[18] and encouraging results have been obtained by a number of authors.[21]

A sudden decrease in the pumping activity of the heart leading to decrease in both flow and pressure, such as in cardiogenic shock (myocardial infarction), may be corrected by noradrenalin which is released under these conditions and is also beneficial when administered. The favorable effect of noradrenalin is probably partly due to an improved irrigation of the damaged heart which is essential during the first critical period.

If a loss of intravasal fluid has occurred, the immediate drop in blood pressure and flow is normally compensated for to a certain limit by the blood pressure homeostatic mechanisms, involving an activation of the vasoconstrictor noradrenalin producing system. Only if this is exhausted, or else ineffective, may exogenous noradrenalin be expected to assist in raising the blood pressure by reducing the volume of the vascular tree and by increasing the resistance.

The usefulness of noradrenalin in such conditions may be inferred from the fact that it is normally released in these situations not only by the adrenergic nerves but also by the suprarenals.

In the first stages of shock, vasoconstriction is generally encountered and should be expected. However, there is often a tendency for the vasomotor response to become less efficient with time, and in such conditions infusion of noradrenalin might help to maintain vascular tone. A drug which tends to dilate the muscle vessels like adrenalin is less appropriate for the purpose of safeguarding the flow in important organs. It is clear that the condition outlined above would be more easily dealt with if the fluid loss is compensated for by infusion of blood or a plasma expander. However, the circumstances are not always such as to allow a rapid and adequate substitution of fluid. Even restitution of the blood volume may not always be effective in raising the blood pressure, as is frequently observed. Noradrenalin may then serve as a pharmacologic crutch—to use the fitting expression of Tainter—during a critical period.

By using isotope labeled red blood cells, Nylin and Pannier [22] have shown that mixing may be very slow in circulatory insufficiency, indicating pooling of blood.

Obviously the effectiveness of noradrenalin in restoring a low blood pressure is dependent upon the responsiveness of the vessels. Unfortunately, this may deteriorate gradually during states of prolonged low pressure and inadequate flow. The reasons for this may be manifold: toxic products, anoxia, lack of conditioning or permissive factors like cortical hormones have to be taken into consideration. Under such conditions noradrenalin may be inefficient, but this would probably apply to all drugs of this kind. It is therefore of paramount importance that the therapy be instituted at a time when the vessels still react.

The intense vasoconstrictor action of noradrenalin has also prompted its use as an adjuvant in local anesthesia. In this respect it is almost as active as adrenalin but possesses certain advantages in that it causes

almost none of the disturbing side actions of adrenalin, such as tachycardia, apprehension and irritability.

In spinal anesthesia it is possible to prolong the duration of the anesthesia by about 100 per cent if 0.5 mg. noradrenalin is added to the analgesic drug. This effect is due to vasoconstriction in conjunction with slow resorption, and it is not followed by any untoward actions as judged by the experience from 1,000 cases [19] (figure 5).

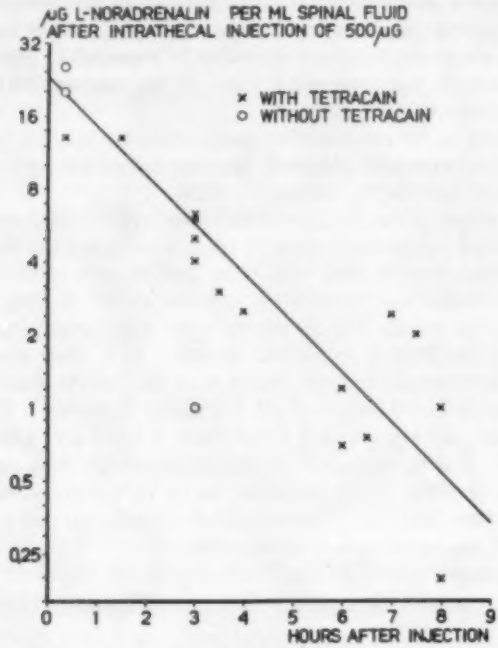

FIG. 5. Noradrenalin in µg./ml. spinal fluid, different times, after intrathecal injection of 0.5 mg. with and without Pontocaine in man. (From S.-O. Liljedahl and U. S. von Euler, Acta Chir. Scand., in press.)

Summarizing, we may say that the explanation of the beneficial effects of noradrenalin in many conditions is still incomplete, partly owing to our unsatisfactory knowledge of circulation during hypotensional states. Noradrenalin is not a panacea which can be expected to give striking results in all kinds of hypotension. On the other hand, it represents a safe and efficient means of restoring a falling blood pressure in many situations where the low pressure is a vital indication, and the release from the natural sources is insufficient.

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RENAL TUBULAR FAILURE OF SHOCK AND NEPHRITIS *

By Donald D. Van Slyke, *Upton, N. Y.*

The manner in which tubular injury can cause excretory failure was observed by A. N. Richards in 1929.[1] He watched through a microscope the nephrons of frogs that had been poisoned with sublethal doses of mercuric chloride, bichromate and other nephrotoxic poisons. Blood circulation and filtration in the glomeruli went on at a normal rate, but the entire filtrate was reabsorbed in the tubules, with resultant anuria. Richards concluded: "The only explanation which I can reach is that, under these conditions, the osmotic pressure of the blood proteins is unobstructed by the normal qualities of the tubular epithelium and is able to draw all, or nearly all, of the glomerular filtrate back into the bloodstream."

General recognition of the clinical importance of tubular failure may be said to date from the observations of Bywaters [2, 3] and his colleagues on the "crush syndrome" in the bombing of London during the early years of World War II. People injured and in shock could recover from the shock and regain good general condition, but continue with anuria, or oliguria with dilute urine, and after some days pass into uremic coma. Bywaters and Dible [4] stated: "In those of our fatal cases where adequate biochemical investigation was made, the urine was a dilute fluid showing poor concentration of urea and little reabsorption of chlorides. These characters are those of a poorly concentrated glomerular filtrate and suggest that there is a failure of the tubules to carry out their function. Such a finding agrees with the histological picture, which is in the main tubular. . . . There may be excessive and unselective reabsorption of the glomerular filtrate through the tubules, leakage back into the blood stream."

Presently it became recognized that similar renal failure could follow shock from battle injury. Dr. E. D. Churchill [5] wrote from North Africa: "By excellent surgery, and the liberal use of whole blood transfusion as well as plasma, we are saving lives, but also keeping certain men alive temporarily only to display later kidney damage. There has been either complete anuria with death, or in one case a fall of urinary output to 200 c.c. with ultimate recovery of kidney function. This phenomenon is not unique to the 'crush syndrome,' but may occur in any wounded man who experiences a long period of greatly reduced volume flow."

Studies begun during the war, and since continued, have shown that this type of renal failure occurs in a great variety of clinical conditions which

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have in common one factor, decrease, lasting usually for several hours, in the volume of circulating blood, usually to such an extent that signs of shock develop, such as bloodless skin, cold extremities and prostration. The condition may occur from hemorrhage, from loss of blood fluid into traumatized areas (the "crush syndrome"), from burns, from the desiccation of vomiting, dysentery or diabetic coma, or from cardiac failure. Organic renal damage is evidenced by failure of renal function to recover when the general circulation is restored. Functional and histologic evidences both indicate that the organic damage is tubular. The functional effect may vary from the degree indicated by a moderate decrease in urea clearance to anuria ending in uremic coma. Complete recovery of renal function may occur over a period of days or months. In a general hospital cases of tubular failure may exceed in number other types of renal disease.

The histological and functional features of the shock kidney had been in part described earlier, during and after World War I, by a number of investigators (see reviews in the papers by Brun,[6] Burch and Ray[7] and Wiggers[8]), but had been generally forgotten or overlooked until Bywaters and his collaborators reopened the field.

Various terms have been used for the condition: "crush syndrome" (Bywaters[2]), "lower nephron nephrosis" (Lucké[9]), "acute tubular necrosis" (Bull[10]), "acute anuria" (Brun[6] and Oliver et al.[11]), "shock kidney" (Van Slyke[12]). Except for "crush syndrome" and "shock kidney," these terms apply also to the practically identical tubular failure caused by nephrotoxic poisons, as well as to the failure caused by conditions involving shock.

One result of the attention drawn to tubular failure resulting from shock is an increased appreciation of the part played by tubular failure in acute and chronic nephritis, and a recognition of results attainable by régimes aimed at ameliorating the effects of tubular failure in these conditions.

The recognition, study and treatment of tubular failure have developed to an important degree from application of renal physiology, exemplifying Haldane's dictum: "The physiology of today is the medicine of tomorrow." We shall briefly review some of the physiologic conceptions that have been applied.

Rôles of Glomeruli and Tubules in Renal Excretion

Since the appearance of Cushny's *The Secretion of the Urine* in 1917,[13] the "filtration-reabsorption" theory has provided the working hypothesis for a large part of the research done on the physiology of the kidney, and has formed a picture into which an otherwise disconnected mass of facts could be fitted in logical order. According to this theory, as the blood courses through the glomeruli, at a rate in adult man of about a liter per minute, about one fifth of the plasma water with its dissolved crystalloid solutes is filtered out and passes down the tubules. In the tubules there

occurs a reabsorption of enough water to maintain the extracellular fluids at their normal volume, and enough of the various crystalloids to maintain their individual concentrations in the extracellular fluid constant within extraordinarily narrow limits.

Tubular Reabsorption

The tubules divide the constituents of the glomerular filtrate into three classes: (1) those that the organism needs to retain as completely as possible, such as glucose and amino acids, which are reabsorbed almost completely; (2) those constituents of the glomerular filtrate which must be reabsorbed in varying amounts to retain exactly enough to preserve the constant volume and electrolyte of the extravascular body fluid—such are the water and the electrolytes; (3) those metabolites for which the organism has no further use, such as urea, uric acid and creatinine, which are rejected and excreted.

The renal tubules, in order to reabsorb selectively the filtrate constituents of the second group, to maintain constant volume and composition of the "milieu interieur," must receive messages from other parts of the body. These messages are at present not completely understood, but it is known that some of them are in the form of hormones. The pituitary secretes a hormone that stimulates reabsorption of water; when this hormone is lacking, diabetes insipidus results, with a flow of urine that may exceed 20 L. per day and result in dehydration of the body unless water intake keeps pace with such an output. Adrenal cortical hormones, at least partly controlled in their output by the pituitary, regulate the activity of the tubules with regard to reabsorption of sodium and potassium; in Addison's disease the deficit of messages to the tubules in the form of this hormone or hormones results in uncontrolled excretion of sodium and resultant sodium deficit in the extracellular fluid, which is responsible for part of the symptoms of the disease.

The brilliant experiments of A. N. Richards and his school have provided an important part of the evidence confirming the filtration-reabsorption theory and showing details of glomerular and tubular functions. Richards, with Wearn, Montgomery, Walker, and other collaborators,[14, 15] developed a series of extraordinary methods for ultramicro-analysis of the constituents of the blood plasma. These investigators also developed a technic whereby they could puncture a single glomerulus or different portions of the tubule of a nephron and withdraw the glomerular filtrate as it was formed. With their ultramicro methods of analysis they could determine the constituents of the glomerular filtrate in volumes as small as one cubic millimeter. They showed that chloride, bicarbonate, creatinine, urea, uric acid, pH and glucose in the glomerular filtrate thus obtained had practically the same concentration as in the plasma. Thus, they demonstrated by direct analysis that the glomerular filtrate in truth is a filtrate of the plasma. Analyses of filtrate from the tubules showed that in the proximal tubules an isosmotic reabsorp-

tion of a large part of the filtrate and part of its solutes occurred; increase in osmolar concentration by selective reabsorption of water occurred in the loop of Henle or the distal tubule. These data were marshalled by Richards [14] 16 years ago in his Croonian Lecture, and more have been added since, especially by Walker and Oliver,[15, 16] who have extended the technic to mammalian nephrons.

One of the objections earlier raised to the filtration-reabsorption theory was that the theory requires the filtration and reabsorption of unbelievably great volumes of water, about 170 L. per day by the adult man. However, Walker, Bott, Oliver and MacDowell,[15] using Richards' procedure for direct catheterization of the tubules, were able to show in 1941 that in mammalian kidneys the amount of fluid passing from the glomerulus into the proximal tubule was equal to that required by the filtration theory, and that at least two thirds of the water with an osmolar equivalent of electrolytes and all of the sugar were reabsorbed before the end of the proximal segment was reached. The finer regulation of water and electrolyte output appears to occur in the more distal parts of the tubule, where the fluid becomes urine with usually greater osmolar concentration than the plasma.

Tubular Function in Maintaining the Body's Acid-Base Balance

One of the functions of the kidney is to maintain a normal pH and a normal bicarbonate reserve in the plasma and in the interstitial fluids. In man and in carnivorous animals there is ordinarily more acid than alkali formed by the metabolism. If the surplus acid in the forms of sulfuric, phosphoric and other acids were not got rid of, their accumulation would cause progressive decrease of the bicarbonate reserve of the plasma and interstitial fluids, and a fall of pH to a fatal level. To prevent such a catastrophe the kidney makes use of at least three functions, all of which are located in the tubules.

1. *Reabsorption of Bicarbonate and Alkaline Phosphate.* The first is reabsorption of bicarbonate and of alkaline phosphate, of the type of Na_2HPO_4, from the glomerular filtrate by the tubules. The amount of bicarbonate filtered by man per day is estimated at about 400 gm., and the amount ordinarily in the 24-hour urine is only about 0.2 gm.

2. *Excretion of Free Acid, or Exchange of H^+ for Na^+ and K^+ in the Tubules.* A second mechanism for getting rid of acid is either the actual excretion of free acid by the tubular epithelium, or the exchange of hydrogen ions by the epithelial cells for ions of sodium and potassium from the glomerular filtrate in the lumina.[17] Montgomery and Pierce [18] have shown that in the amphibian kidney the fall in pH occurs in the distal tubule (figure 1).

3. *Excretion of Ammonia Formed in the Kidneys.* The third mechanism whereby the kidneys protect the organism from acid intoxication is the

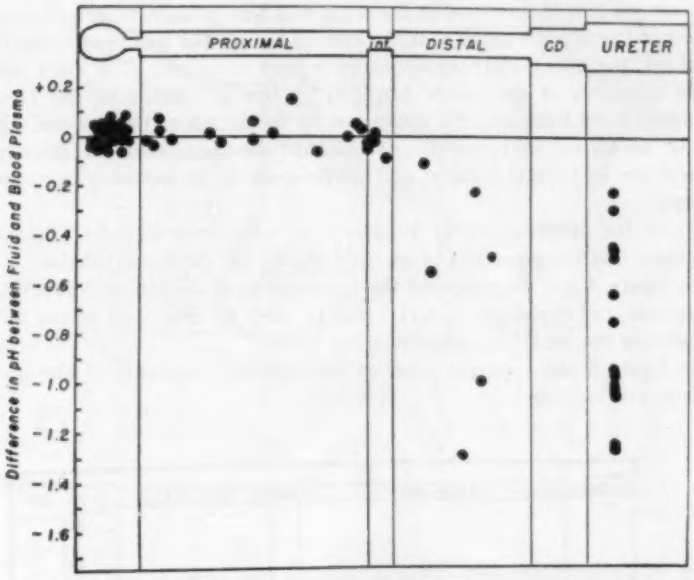

FIG. 1. pH of fluid withdrawn from different sections of amphibian tubules. From Montgomery and Pierce.[18]

formation and excretion of ammonia. In conditions of acidosis the amount of ammonia excreted is usually much greater than the titrable acid. In diabetic acidosis ammonia formation is the chief defense against fatal intoxication. The ammonia is formed in the kidney itself. This was shown by Nash and Benedict,[19] who demonstrated in dogs with acidosis that the

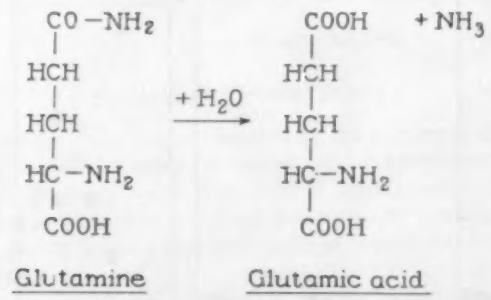

FIG. 2. Hydrolysis of glutamine by gutaminase.

ammonia content of the blood in the renal vein was greater than the ammonia content in the arterial blood. If the excreted ammonia had been taken from the blood, the above relation would have been reversed. The chief source of the ammonia is the amide nitrogen of free glutamine in the blood.[20] Ammonia is set free from the glutamine by the action of the enzyme, glutaminase, as shown in figure 2. Archibald[21] demonstrated the activity of glutaminase in normal kidneys and its decrease to almost zero in nephritic kidneys.

From the observations of Walker[22] on amphibian kidneys (figure 3) it appears that the ammonia is secreted chiefly by the distal tubules.

In figure 4 are diagrammed the apparent mechanisms of $NaHCO_3$ reabsorption, and exchange of NH_4^+ and H^+ ions for Na^+ ions of the filtrate to maintain the $NaHCO_3$ reserve of the body.

In figure 5 the apparent rôles of the different segments of the human nephron are indicated.

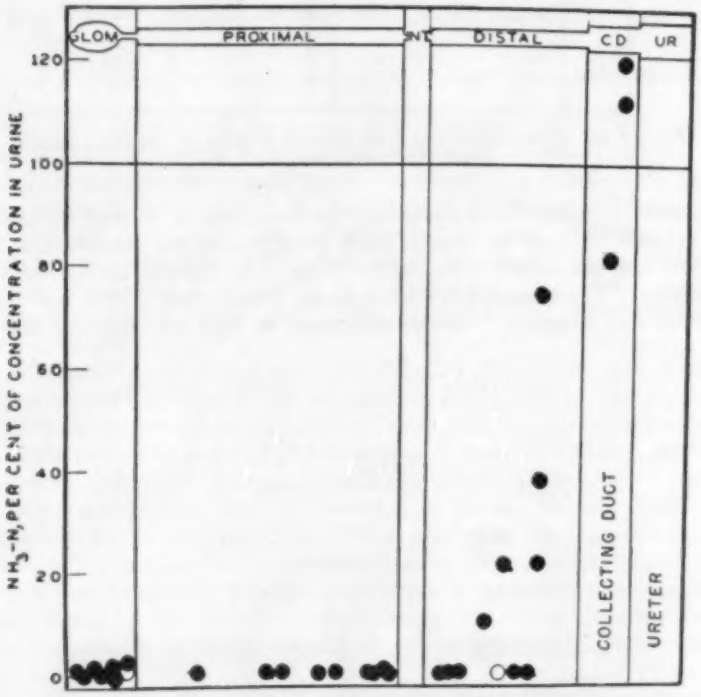

FIG. 3. Concentrations of ammonia in tubular fluid drawn at various levels from amphibian tubule. From Walker.[22]

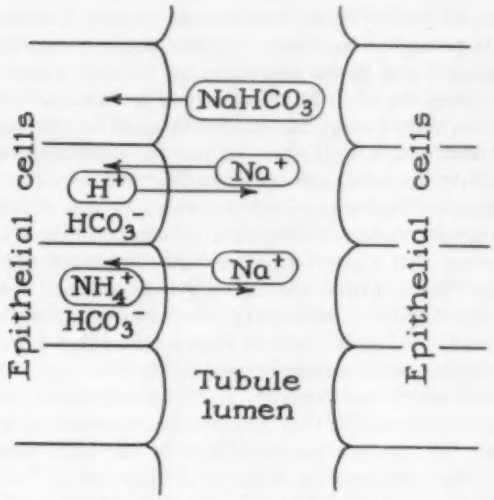

FIG. 4. Ion exchange in tubule to maintain bicarbonate reserve of the body.

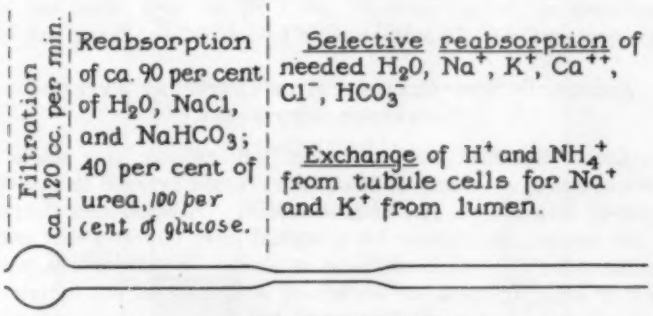
Filtration ca. 120 cc. per min.
Reabsorption of ca. 90 per cent of H2O, NaCl, and NaHCO3; 40 per cent of urea, 100 per cent of glucose.
Selective reabsorption of needed H2O, Na+, K+, Ca++, Cl−, HCO3−
Exchange of H+ and NH4+ from tubule cells for Na+ and K+ from lumen.

FIG. 5. Diagram of tubular functions.

EXCRETION BY THE TUBULES

In mammals the processes of filtration by the glomeruli and selective reabsorption by the tubules appear to constitute the mechanism by which the composition of the body fluids is ordinarily maintained. However, there are aglomerular animals [23] in which all the excretory work is carried on by tubules alone, and it appears that the power of tubular excretion is retained by mammals, although used to a significant extent only to eliminate foreign substances, or to assist in elimination of normal excretory products under unusual conditions. One might consider tubular excretion as a hereditary reserve which can upon occasion be called into action. Thus, in the case of

potassium there is ordinarily no evidence of tubular excretion; but when large amounts of potassium have been administered to a dehydrated subject,[24] or in renal disease,[25] the potassium clearance may be greater than can be accounted for by glomerular filtration alone, as measured by the inulin clearance, and the excess potassium excretion must be attributed to tubular excretion. In man creatinine, when its plasma concentration is markedly increased, similarly shows clearances exceeding that of inulin.[26, 27]

The most marked examples of tubular excretion are shown in the elimination of foreign substances. One such substance is the dye, phenol red. Marshall [28] showed that about 60 per cent of the phenol red in blood was removed as the blood flowed through the mammalian kidney. Such a complete removal could not be accomplished by filtration alone. In fact, very little of the dye exists in the free state in the plasma, most of it being bound to the proteins, so that little is presumably filtered. Other substances have been found which are removed so completely from the renal blood plasma that one must conclude that they also are removed by active secretion by the tubules. The proportion of hippurate extracted from the plasma by the kidneys was measured in dogs by Phillips et al.,[29] and in men by Warren et al.,[30] by comparing the concentration of hippurate in the arterial plasma with the concentration in renal venous plasma, and was found in both dogs and men to average normally about 90 per cent, when the arterial plasma concentration of the substance did not exceed 4 or 5 mg. per 100 c.c.

Significance of Clearances of Different Types of Excretory Substances

The term "clearance" was introduced [31] to indicate in a single value, easily visualized as a volume of blood, the relation between the blood concentration of urea and the rate of its excretion. A blood urea clearance of 75 c.c. per minute, the average for a normal man, indicates that excretion in 1 minute clears the urea from 75 c.c. of blood. In other words, a volume of 75 c.c. of blood contains the amount of urea excreted per minute. The clearance concept, first applied to urea, has been fruitfully extended by Homer Smith [23] and his collaborators to express the relation of excretion rates of other substances to their concentrations in blood (blood clearances) and plasma (plasma clearances). Clearance is calculated as R/B, where R is the excretion *rate* in milligrams of substance per minute, and B is the *concentration* of the substance in milligrams per cubic centimeter *in the blood or plasma*. The normal clearances of five substances, and the parts played by glomerular filtration and tubular excretion, are indicated in figure 6.

It will be noted that about 40 per cent of the *urea* filtered in the glomeruli is reabsorbed in the tubules. This reabsorption is attributable, not to active cellular reabsorption, but to back diffusion of the highly diffusible urea from the concentrated tubular urine into the blood. When the urine becomes

highly concentrated (urine volume under about 2 c.c. per minute), the back diffusion of urea becomes even greater than the 40 per cent indicated in figure 6. The reabsorption is explainable by the laws of physical diffusion,[22] with assumption that for urea the coefficient of diffusion through the tubular walls is uniquely low. The kidney would be a more nearly perfect organ if none of the urea diffused back, so that all of that filtered could be excreted. The urea clearance can be pathologically decreased either by decrease in glomerular filtration rate or by an increase in back diffusion through damaged tubules. As will be seen later, depression of urea clearance in clinical renal failure appears to occur from both causes.

Inulin appears to be freely filtered in the glomeruli, and there is evidence that as the filtrate passes down normal human tubules the inulin in it is neither increased by tubular excretion nor diminished by reabsorption. Hence the plasma clearance of inulin may be assumed under normal conditions to equal the glomerular filtrate. For example, if 600 c.c. of plasma perfuse the kidney per minute (figure 6), and 120 c.c. of plasma water with the inulin dissolved in it are filtered in the glomeruli, the inulin excreted per minute will be the amount contained in 120 c.c. of arterial plasma, and the plasma inulin clearance will be 120 c.c., equal to the filtrate volume.

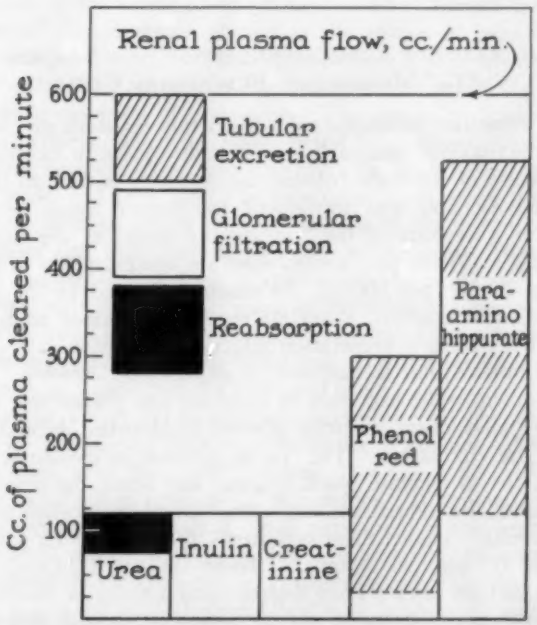

FIG. 6. Clearances of urea, creatinine, inulin, phenol red, and para-aminohippurate in normal adult.

Hence inulin clearances are used as measures of the glomerular filtrate, and are often quoted as "glomerular filtrates."

When *para-aminohippurate* and *Diodrast* are extracted to a normal 90 per cent from the renal plasma, the plasma clearances of these substances approximate 90 per cent of the renal plasma flow, and can serve as a measure of the flow. However, when the tubules are damaged in advanced nephritis, or in the acute renal failure that follows shock or poisoning, as will be shown later, only a small fraction of the para-aminohippuric acid or Diodrast may be extracted, and their clearances are then much less than the renal blood or plasma flow.

All of the excretory substances represented in figure 6 are of the group which the body may be assumed to have no interest in retaining. They are either end-products of metabolism (urea and creatinine) or foreign substances. It is only such substances in general that give clearances that have significance with regard to the excretory capacity of the kidney.

For substances like glucose and the amino acids, which are almost completely reabsorbed to retain their nutritive values, or like the normal electrolytes, that are reabsorbed in the proportions needed to maintain their normal contents in the body, clearance values have no definite significance in terms of excretory capacity.

Maximal Rates of Tubular Excretion and Reabsorption. The "T_m" Measure of Functional Capacity

For each substance which the tubules actively reabsorb or excrete there is a limit to the maximal attainable rate of reabsorption or excretion. This rate is a measure of what the tubules can do when pushed to the limit of functional activity, and was introduced by Homer Smith and his collaborators [22] as a measure of the "functioning mass" of the tubules, symbolized as "T_m". When para-aminohippurate concentration in the plasma exceeds about 20 mg. per 100 c.c. the amount excreted by the tubules per minute reaches a maximum, about 80 mg. for a normal adult. Further increases in the plasma concentration affect the excretion rate only by increasing the amount that is excreted by glomerular filtration. A similar behavior is shown in the excretion of Diodrast and phenol red, and is also shown by the mechanism whereby glucose is absorbed *from* the tubular lumina into the circulation. The T_m of glucose is measured by giving glucose infusions to increase blood glucose, and hence the amount filtered per minute, until the filtered amount cannot be all reabsorbed and massive glucosuria results. Under these conditions the glucose T_m for a normal adult is about 375 mg. per minute.[23] There are also T_m values for amino acids and for sodium salts. They depend upon activity of the tubular cells, and are not mechanical constants, but are somewhat variable under hormonal influences which affect the tubular cells.

The Effects of Shock on Renal Physiology

Shortly after Bywaters' description of the crush syndrome our group at the Rockefeller Hospital was asked to study the phenomenon. It was found that shock produced by hemorrhage or trauma could cause complete cessation of renal blood flow from constriction of the renal vessels. Furthermore, the after-effects of shock on the kidney could be reproduced in all details and degrees by clamping the renal arteries of dogs for varying periods of time. Not only the functional effects were the same, but also the histologic changes in the nephrons. It appears, therefore, that the "shock kidney" is an example of tubular failure, in which damage to the tubular cells is caused by anoxia. The functional results are identical with those caused by nephrotoxic poisons; the histologic changes are similar, though not identical.

In figure 7 are data which permit an analysis of some of the immediate effects of progressing hemorrhage, with ultimate shock, on different parts of the renal function.[29] Similar changes were observed during shock from muscle trauma. The renal blood plasma flows were calculated by Fick's principle from para-aminohippurate extraction and excretion: (ml. renal blood plasma flow per min.) = (mg. PAH excreted per min.)/(mg. PAH extracted from 1 ml. renal blood plasma). The "filtered fraction," viz., the fraction of plasma water filtered in the glomeruli, was calculated as (plasma creatinine clearance)/(renal plasma flow); this calculation appears to be justified as long as tubular damage does not reach the point where it permits back diffusion of creatinine. The curves in figure 7 illustrate the following effects, which were also noted in traumatic shock.

1. General arterial blood pressure may be maintained until a large volume of blood has been lost. In this experiment there was no fall in pressure of the femoral artery until the volume of blood drawn, 44 c.c. per kilo, was about half that originally present in the dog. The maintenance of pressure during such a loss is attributable to peripheral constriction. This constriction, while causing some of the evident signs of shock, such as bloodless skin and cold limbs, nevertheless reduces the volume of perfused vascular bed in proportion to the blood loss so that circulation and arterial pressure can be maintained in the heart and brain.

2. The kidneys may not at first take part in the peripheral constriction, but eventually do so. In this experiment the renal blood (plasma) flow remained normal until the blood loss was 25 c.c. per kilo. With further blood loss a rapid fall in renal blood flow set in. It appeared due to renal constriction, because the femoral blood pressure for the next two hours remained normal, while renal blood flow fell by half. It is as though the kidney decreased its own circulation in order to maintain that of the heart and brain. Since the normal renal blood flow is about 20 per cent of the cardiac output during rest, there is an obvious advantage to the organism

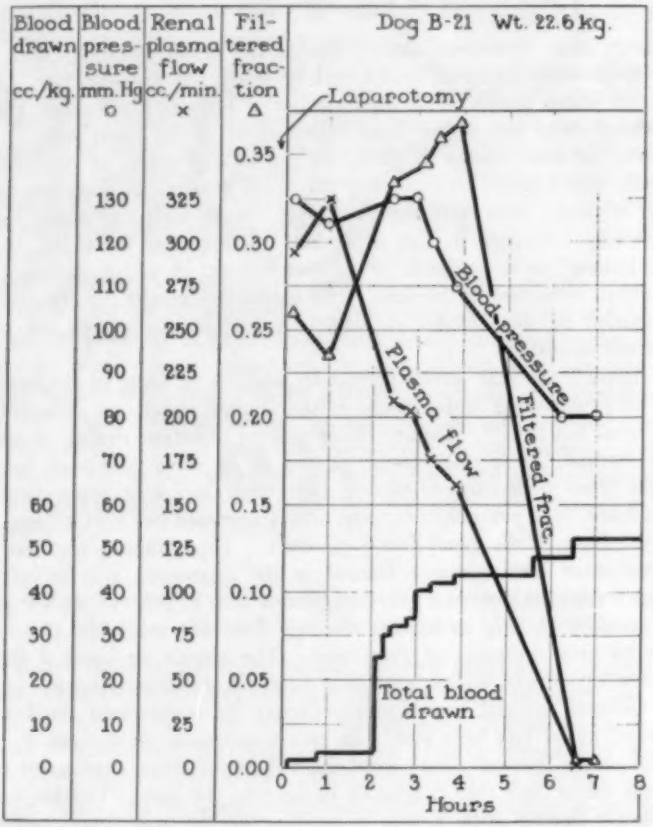

FIG. 7. Renal physiology in shock caused by progressive hemorrhage. From Phillips, Dole, Hamilton, Emerson, Archibald and Van Slyke.[29] Reprinted by permission of the *American Journal of Physiology*.

in a mechanism for commandeering blood from the kidneys in time of vital need.

3. A compensatory effect in maintaining excretion during hours one to four is seen in the marked increase in the filtered fraction during this period, presumably due to efferent constriction.

4. Eventually the sacrifice of the renal circulation may become complete. In this experiment it occurred after the volume of blood drawn was about 48 c.c. per kilo. There was a rapid fall in renal blood flow and excretion of creatinine and hippurate to almost zero. This debacle occurred when the femoral pressure was still over 80 mm., and hence appears to be attributable to renal constriction. All available evidence indicates that it is

such ischemia that injures the tubular cells and causes the tubular failure that follows severe and prolonged shock.

Functional Picture Persisting After Shock

For the post-shock period adequate data are available from observations on patients. As might be expected in tubular paralysis, there is failure in the discriminatory excretion of water and the individual electrolytes required to maintain constant volume and composition of the body fluids. Failure of tubular regulation was noted by Bywaters and his collaborators.[2, 8] It has been studied in detail by the late John Lockwood and his collaborators [22] in postoperative conditions, and by Bull, Joekes and Lowe [10] and Swan and Merrill [24] in post-shock and nephrotoxic conditions. Shock causing renal damage is followed by a period of anuria or oliguria; the small volume of dilute urine (400 ml. or less per day) excreted for a number of days tends to approach plasma ultrafiltrate in electrolyte and urea concen-

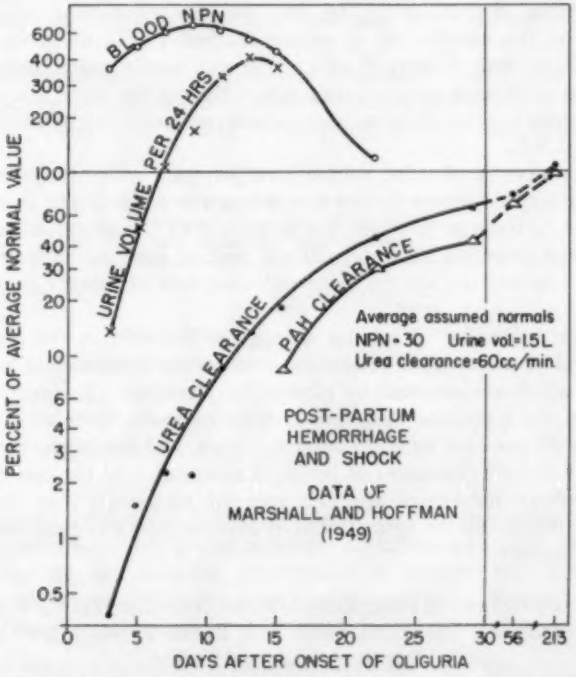

Fig. 8. Chart of patient recovering from hemorrhagic shock. Urea clearance showed progressive improvement from first day of observation, three days after onset. However, excretion was not enough to start descent of blood urea curve for six days, during which observation of blood urea alone would have given the false impression that the renal condition was making no improvement. From Marshall and Hoffman.[35]

trations. Plasma urea and potassium concentrations increase. The slight excretions of water and sodium cannot be increased. Unless their intakes are regulated accordingly, the patient is likely to be overhydrated, with resultant circulatory embarrassment and pulmonary edema. Also, the increase of plasma potassium may endanger the heart. Later, if diuresis develops, there may be indiscriminate output of plasma electrolytes and water, and it becomes necessary to regulate intakes according to blood analyses in order to avoid either excess or deficit in the body.

In figure 8 are charted typical data from a case of renal failure following hemorrhagic shock observed by Marshall and Hoffman,[35] who followed the condition from complete anuria to return of normal function attained after several months. The functional data are plotted on a logarithmic scale in order to make visible the early gains in urea clearance, which started at less than 1 per cent of normal.

The case illustrates the fact that rise of daily urine volume to the average normal of 1.5 L., although a favorable prognostic sign, may not indicate that renal excretion of urea, creatinine, etc., has reached similar recovery. In this case, on the day the urine volume reached 1.5 L. the urea clearance was only 2 per cent of normal; the urine was hardly more than a plasma ultrafiltrate, with urea concentration about that of the blood instead of the fiftyfold greater concentration that would normally accompany a urine volume of 1.5 L.

Further increase of urine volume to a polyuria, which frequently occurs during recovery, is shown in this case where the daily output in two weeks reached 6 L. Even at this time the urinary urea concentration was so low that the urea clearance was only 20 per cent of normal. The inability of the kidneys to concentrate the urine indicates lack of tubular concentrating function.

Another indication of tubular damage is decrease in the clearance of para-aminohippurate out of proportion to decrease in clearances of mannitol or inulin, which are excreted by glomerular filtration. Normally 70 to 80 per cent of the hippurate excretion is believed to be by tubular excretion, only 20 or 30 per cent by glomerular filtration, and the hippurate clearance is several times the clearances of inulin or mannitol. In the case of figure 8 the first para-aminohippuric acid clearance was no greater than the mannitol clearance (not shown on figure), and in another case was even less than the mannitol clearance.

Rôles of Deficient Renal Blood Flow and Deficient Extraction of Excretory Products from the Blood in Renal Failure Persisting after Shock

It appears that both factors, retarded renal circulation and deficient extraction, contribute in varying but important degrees to the renal failure. Bull, Joekes and Lowe [10] have used catheterization of the renal vein to ascertain the proportions of urea, creatinine, and para-aminohippurate extracted.

TABLE 3

PROTHROMBIN TIMES (SECONDS) RELATED TO THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH GENERALIZED ARTERIOSCLEROSIS

	UNDER 19.9	20-24.9	25-30.9	OVER 40	#
RENAL INFARCT	1		1	0	(2)
PULMONARY INFARCT		1	1	0	
CEREBRAL THROMBOSIS		1	1	0	

NOT ON DRUG

tients were hypertensive. In 248 months and 13 days before anticoagulant therapy 48 thromboembolic episodes occurred, 25 of which were cerebral. During 287 patient months (a longer period) of anticoagulant therapy the same patients suffered only eight thromboembolic episodes, of which two were cerebral, as in the cases of old rheumatic heart disease—a striking reduction.

The distribution according to location of complications before and after anticoagulant therapy is shown in table 4. As in patients with rheumatic heart disease, there is a striking relationship between the recurrence of

TABLE 4

THROMBOEMBOLIC EPISODES IN 19 PATIENTS WITH GENERALIZED ARTERIOSCLEROSIS

	BEFORE ANTICOAGULANT THERAPY	AFTER ANTICOAGULANT THERAPY
CEREBRAL VASCULAR	25	2
MYOCARDIAL INFARCTION	13 (IN 8 PATIENTS)	0
RENAL INFARCT	2	4 (1)
PULMONARY	2	2
PERIPHERAL	6	0

thrombo-embolic incidents and the intermittent use of anticoagulants. There were seven patients in this group in whom anticoagulants were used intermittently, and in each instance interruption of therapy was followed by recurrence of thrombo-embolic complications. The following illustrate graphically these relationships.

Patient 9 is a 53 year old white male who at the age of 50 experienced his first myocardial infarction, which was mixed in type. He was admitted to New York Hospital and anticoagulants were begun July 20, 1950, effective levels being reached within 72 hours, but dropping below therapeutic levels on six occasions. The patient made a satisfactory recovery and was discharged after 30 days. Anticoagulants were

discontinued at that time. Seven months later the patient suddenly developed pain and coldness in the left lower extremity from the knee down; anticoagulants were not given. Eleven months after this episode he developed evidence of a left hemiparesis which was transient, the only residual being a left facial weakness. Eight months later the second myocardial infarction occurred in the posterior base, and the patient was again placed on anticoagulants, this time for 40 days. On discharge, anticoagulants were again discontinued and three months later he developed sudden coldness and pain in the entire right lower extremity; an embolus was removed from the right femoral artery and anticoagulants were re-instituted. The patient has remained under this therapy since that time (11 months, 20 days) without further incident.

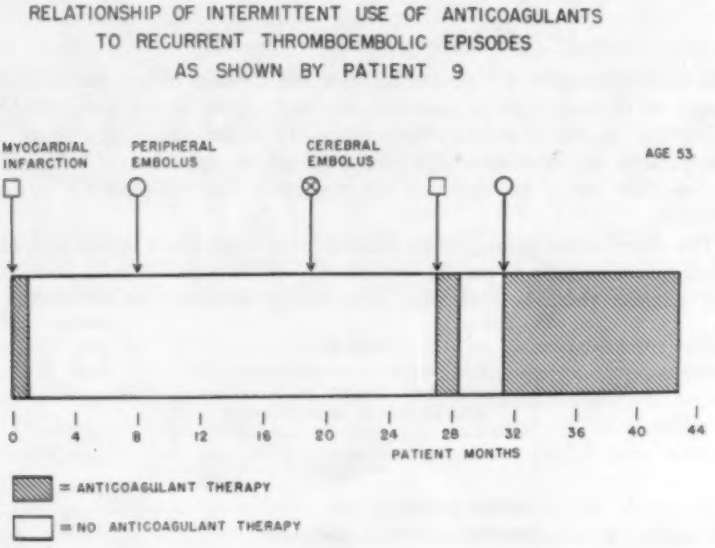

FIG. 1.

Patient 52, a 54 year old white female with known hypertension for 10 years, in 1950 had two myocardial infarcts requiring hospitalization, but no anticoagulants were given. In July, 1951, she was admitted to New York Hospital for anticoagulant therapy following embolization to a digital artery of the right third finger. Anticoagulants were employed, and she was discharged on anticoagulants, on which she continued for 46 days. Because of difficulty in traveling, the patient discontinued therapy. Seven months later she was re-admitted with another myocardial infarct and anticoagulants were resumed. She remained on anticoagulants until October 31, 1952, when she was readmitted because of severe epistaxis and evidence of a pulmonary infarction. Stool examinations at this time were guaiac positive. The prothrombin time was 35.5 seconds. Anticoagulants were discontinued. Ten days later she developed evidence of a left hemiparesis. During the three weeks preceding this admission three of the six determinations were below the therapeutic range and may have been a contributory factor in the pulmonary infarction which followed. The patient made a satisfactory recovery and was followed by the home care service

RELATIONSHIP OF INTERMITTENT USE OF ANTICOAGULANTS
TO RECURRENT THROMBOEMBOLIC EPISODES
AS SHOWN BY PATIENT 52

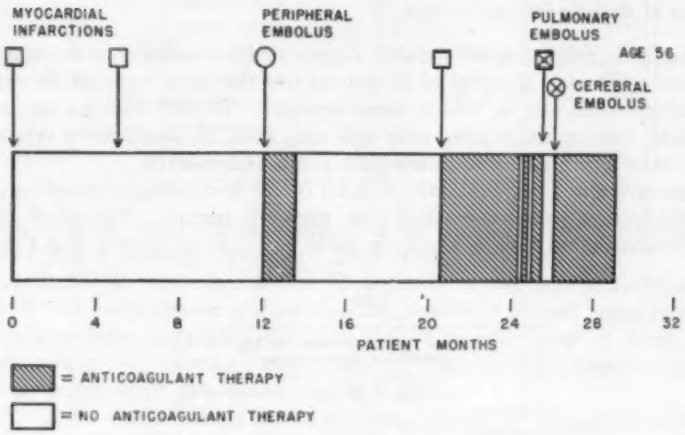

FIG. 2.

RELATIONSHIP OF INTERMITTENT USE OF ANTICOAGULANTS
TO RECURRENT THROMBOEMBOLIC EPISODES
AS SHOWN BY PATIENT 20

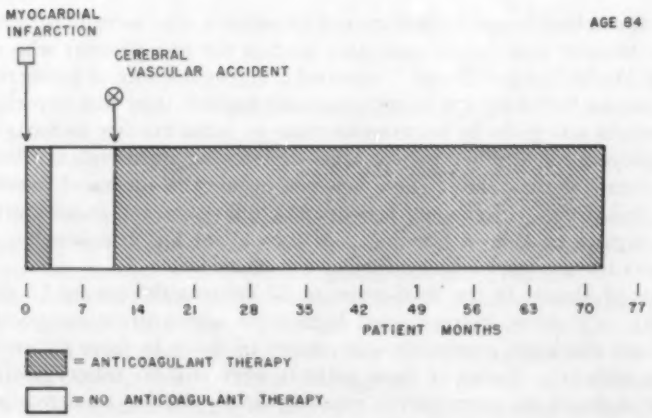

FIG. 3.

of New York Hospital for three months, remaining on anticoagulants during this period.

Patient 20 is an 84 year old white female who had a myocardial infarct in March, 1947. She was hospitalized for three months, receiving anticoagulants during that period. Eight months later she had a cerebral thrombosis and was again started on anticoagulants. She has now been on anticoagulants for 62 months, without further evidence of thrombo-embolic incident.

The final group of seven patients represented a number of miscellaneous diagnoses. During a period of 83 patient months there were 20 thrombo-embolic episodes, 10 of which were cerebral. In 165 months on anti-coagulant therapy there were four episodes, none of which were cerebral, and none of which occurred at adequate prothrombin levels.

Hemorrhagic Complications: A total of 29 hemorrhagic complications occurred in nine patients, most of them minor in nature. The relationship to the prothrombin time is shown in table 5. It is of interest that the in-

TABLE 5

PROTHROMBIN TIMES (SECONDS) RELATED TO HEMORRHAGIC COMPLICATIONS

	UNDER 19.9	20-24.9	25-39.9	OVER 40	UNKNOWN
HEMATURIA	1	1	1	4	
CEREBRAL HEMORRHAGE		1*		1	1*
EXCESSIVE MENSTRUAL FLOW			1		
MELENA			2	1	
EPISTAXIS			1		
ECCHYMOSIS		1	3	1	2
HEMOPTYSIS		1	3*	1	

‡ HEPARIN * ASSOCIATED WITH PULMONARY INFARCTION

stances of cerebral hemorrhage occurred in patients who were hypertensive, and that heparin was the anticoagulant used in the two patients who died. Recently MacMillan and Brown [10] reported a higher instance of hemorrhagic manifestations following use of intramuscular heparin than that experienced when heparin was given by intravenous route or when another anticoagulant was employed. The other patient who experienced intracerebral bleeding made a complete recovery. There was one instance of increased menstrual flow in this group. Following a diagnostic dilatation and curettage there was no further episode of bleeding, and the patient has remained on anti-coagulants for six years with no further complications.

Cause of Death: In the total series of 57 patients there were 13 deaths (table 6). Of these, two occurred because of hemorrhagic complications as has been discussed previously (the causes of death in these patients are listed in table 6). Seven of these patients were still on anticoagulants at the time of death, the complication resulting fatally, having occurred during a period when anticoagulant levels were inadequate. Four patients were

TABLE 6

CAUSE OF DEATH		
	CEREBRAL VASCULAR DISEASE	RHEUMATIC HEART DISEASE WITH EMBOLIZATION
CONGESTIVE HEART FAILURE	4	
CEREBRAL HEMORRHAGE	1	1
CEREBRAL EMBOLI		1
CEREBRAL THROMBOSIS	1	
FRACTURED HIP	1	
POSTVALVULOTOMY VENTRICULAR TACHYCARDIA		1
PULMONARY EMBOLI		3

under adequate anticoagulant therapy at the time of death, the immediate cause of death, however, being unrelated to such therapy.

It should be remembered that all patients in this series were patients with severe heart disease and/or vascular disease, suffering from recurrent thrombo-embolic complications. The risk of complications of many types is inherent in the natural history of such disease, and complications are not therefore necessarily due to anticoagulant therapy.[9]

From the experience gained in studying this group of patients it is evident that anticoagulants may be utilized in the treatment of patients who

TABLE 7

SUMMARY			
NUMBER OF PATIENTS	PATIENT MONTHS	TOTAL THROMBO-EMBOLIC EPISODES	CEREBRAL VASCULAR
BEFORE ANTICOAGULANT THERAPY			
57	795	209	81
DURING ANTICOAGULANT THERAPY			
57	1162	23	6

have had cerebral vascular accidents due to thrombo-embolic complications. The precautions in the use of these drugs have been adequately discussed in previous communications from our group and many others.

The number of thrombo-embolic episodes actually occurring exceeds those diagnosed clinically. This has been confirmed by the report of necropsy material made by the Committee on Anticoagulants of the American Heart Association.[11] These findings were further substantiated in a group of 98 patients coming to necropsy with diagnoses of cerebral hemorrhage, cerebral thrombosis and embolism during the years 1942 to 1952

on the Second Medical (Cornell) Division of Bellevue Hospital (table 7). Of the 46 patients with anemic infarcts due to either thrombosis or embolism, 23 (50%) exhibited evidence of 50 major thrombo-embolic complications other than those occurring in the brain. These included pulmonary emboli, myocardial infarction, occlusion of the inferior vena cava, femoral vein, renal artery and the lower abdominal aorta. In many instances the immediate cause of death was thought to be the thrombo-embolic complication.

Fifty-two of these patients had evidence of hemorrhagic involvement in the brain. In 17 of these there were, in addition, 23 major thrombo-embolic complications. From these observations it seems reasonable to assume that these episodes represent the manifestation of a severe disturbance in the clotting mechanism, which may result in hemorrhage of clotting or even both simultaneously, and which is strongly influenced by

TABLE 8

MAJOR THROMBOEMBOLIC EPISODES IN 98 PATIENTS WITH CEREBRAL VASCULAR DISEASES AUTOPSIED AT BELLEVUE HOSPITAL, 1942 - 1952

TOTAL NUMBER OF PATIENTS	DIAGNOSIS	PATIENTS WITH COMPLICATIONS	NUMBER OF MAJOR THROMBOEMBOLIC COMPLICATIONS
46	CEREBRAL THROMBOSIS OR EMBOLISM	23	50
52	CEREBRAL HEMORRHAGE	17	23

local factors affecting the endothelial lining of the vascular system. These factors are as yet incompletely understood.

Value of Anticoagulants in the Treatment of Cerebral Vascular Accidents: It is difficult or impossible to obtain *conclusive* evidence which indicates that the use of anticoagulants has influenced the immediate course of a specific patient after a cerebral vascular accident has occurred.[12] It is, however, the impression of numerous observers that a favorable influence has been exerted. To accumulate additional evidence regarding this point a comparable group of control and treated patients must be studied; such a study is now in progress.

SUMMARY

1. Cerebral vascular diseases are among the most serious and common diseases.

2. The present state of knowledge of these diseases and the present results of treatment are far from satisfactory.

3. Differential diagnosis is no longer of purely academic interest, and various methods to aid in diagnosis have been discussed and evaluated.

4. Vasospasm occurs in the cerebral arteries and is of importance in terms of warning of more serious phenomena to come, and also because treatment may be of some help in preventing the serious sequences.

5. Cerebral hemorrhage is always serious. Surgical methods may be seriously considered for some subdural or extradural hemorrhages. Most other cerebral hemorrhages are not amenable to specific therapy at this time.

6. The use of sympathetic blocks for acute thromboses or emboli is under study at present; final evaluation remains for the future.

7. The use of anticoagulant drugs for the treatment of thrombosis and embolism is also in the process of investigation. Their trial appears justified, but future experience is essential for final evaluation.

8. Experience with the use of anticoagulants in the reduction of thrombo-embolic episodes in 57 patients treated for a total period of 1,162 months is summarized.

9. Fifty-seven patients during a period of 795 patient months before beginning anticoagulant therapy experienced 205 thrombo-embolic episodes, 81 of which were cerebral in location. Following institution of anticoagulant therapy, during a period of 1,162 patient months, these patients experienced 23 thromboembolic episodes, six of which were cerebral in location.

10. The reduction appears to occur in emboli arising from thrombi in the hearts of patients suffering from rheumatic heart disease or from acute myocardial infarction.

11. A reduction in the incidence of recurrent thromboses in the arteries of the brain has also been noted.

12. The risk from hemorrhage in the treatment of these diseases with anticoagulants is present but not excessive.

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PHYSIOLOGIC BASIS FOR THE CLINICAL USE OF NORADRENALIN *

By U. S. von Euler, F.A.C.P. (Hon.), M.D., *Stockholm, Sweden*

The therapeutic use of noradrenalin was suggested by Biberfeld [3] in Austria half a century ago because of its strong vasoconstrictor action and low toxicity, but his plea for the new drug evoked no response, and interest in noradrenalin as a drug was almost negligible before the late forties. Since that time the number of investigations dealing with its therapeutic applications has grown rapidly.

Probably the most valuable and informative basis for the rational use of noradrenalin is its function as sympathetic nerve transmitter and suprarenal medullary hormone.[5, 6, 16] Incidentally, the old claim that the so-called natural adrenalin from suprarenal extracts was superior to the synthetic compound may have been due to the admixture of some 20 to 30 per cent noradrenalin in the natural product.

Although the activities of noradrenalin in the body are as manifold as the functions of the adrenergic nerve system, chiefly the circulatory actions will be considered for the present purpose.

The evidence that noradrenalin serves as the adrenergic nerve transmitter is by now thoroughly established. Thus noradrenalin is present in all adrenergic nerves and in organs supplied with such nerves, notably in the spleen, heart and blood vessels. The nerve-free placenta lacks noradrenalin (figure 1).

Small amounts of adrenalin are found in extracts of nerves and tissues also, but there is so far no evidence that adrenalin is produced by adrenergic nerves. The adrenalin may well be derived from chromaffin cells present in the organs. This assumption is supported by the fact that after adrenergic nerve degeneration the noradrenalin disappears or is reduced to a higher degree than the adrenalin. On regeneration of the adrenergic nerves noradrenalin reappears.[14] In its rôle as mediator of vasomotor action noradrenalin is the primary regulator of the blood pressure, and its action on the vascular system and the heart determines the efficiency of the blood pressure homeostatic mechanism. We do not know whether a generalized reflex vasomotor action is identical in its action pattern with that of an intravenous infusion of the drug, but there are reasons to believe that the differences, if present, are not very large. After the release at the adrenergic nerve endings most of the noradrenalin is locally destroyed, probably partly by amine oxidase, but some escapes into the blood stream and is excreted through the urine.

* Presented as the Lilly Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

The general circulatory actions of the drug have been largely elucidated by the studies of Goldenberg and his co-workers in 1948.[19] By using continuous infusions in man they found that doses from 0.05 μg. per kilogram per minute and higher raise both the systolic and the diastolic blood pressure. Since the cardiac output does not change, this means an increased peripheral resistance due to vasoconstriction. The heart frequency in man is reduced as a result of reflex vagal action, which conceals the positive chronotropic effect. This reflex, which is elicited by the stretch receptors of the carotid sinus and aorta, is abolished by atropine. Noradrenalin also exerts a strong positive inotropic effect. The coronary vessels are dilated, allowing an increased blood flow to the heart muscle.

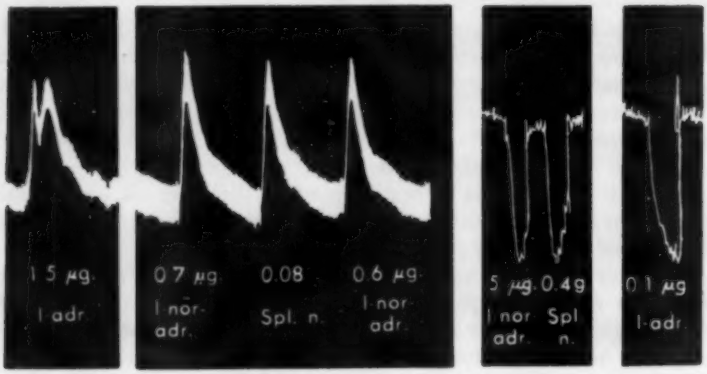

FIG. 1. Blood pressure, cat. Effect of 1.5 μg. adrenalin, 0.7 μg. noradrenalin, 0.08 gm. extract of splenic nerves (cow), 0.6 μg. noradrenalin. Fowl's rectal cecum. Effect of 5 μg. noradrenalin 0.4 gm. splenic nerves and 0.1 μg. adrenalin. (From Thudichum Memorial Volume, by courtesy of Charles C Thomas, Publisher.)

The actions of noradrenalin are different from those caused by adrenalin, which in moderate amounts in man causes vasodilatation as a net effect. Adrenalin does not raise the diastolic pressure to the same extent as the systolic pressure. The mean effective pressure thus may be considerably lower with adrenalin than with noradrenalin, even when the systolic pressure is the same.

Both adrenalin and noradrenalin constrict the cutaneous and part of the splanchnic vessels, but they differ markly as regards the muscle blood flow. This is usually decreased by noradrenalin but considerably increased by adrenalin.[1]

The blood vessels to the liver,[2] the kidney [27] and the brain [28] are constricted by moderate doses of noradrenalin, but usually this effect is nearly compensated for by the increased pressure head.

The redistribution of the blood in the body during infusion of moderate doses of noradrenalin thus seems to be relatively moderate, and in most

organs of greater importance the flow is not impaired in spite of the vasoconstriction. This is what should be expected if noradrenalin is the primary regulator of the blood pressure level. With adrenalin, on the other hand, vasodilatation occurs not only in the heart but also in skeletal muscle and in the liver, and in spite of an increased total output of the heart the effective mean pressure head is lower. Since the vasoconstriction may be as intense in some organs as with noradrenalin, the flow in these organs will consequently be reduced. This is the case in the skin, where it is of little concern, but it may also occur in the kidney.

Direct measurements of the venous return in open-chest anesthetized dogs subjected to various procedures causing a change in the peripheral resistance, including administration of noradrenalin, have shown that the venous return changed in the same direction as the peripheral resistance.[23] The effect is interpreted as a result of active changes in the post arteriolar blood vessels, most likely the veins.

TABLE 1

Effect of Adrenalin and Noradrenalin on Various Vascular Regions

	Adrenalin	Noradrenalin
Skin Vessels	Constr.	Constr.
Kidney Vessels	Constr.	Constr.
Brain Vessels	(Constr.)	(Constr.)
Lung Vessels	(Constr.)	(Constr.)
Muscle Vessels	Dil.	(Constr.)
Liver Vessels	Dil.	Constr.
Heart Vessels	(Dil.)	Dil.

Brackets denote weak or inconsistent action.

Table 1 shows the effect of noradrenalin and adrenalin on various vascular regions.

The fact that the pulmonary, the muscular and the cerebral vessels are relatively insensitive to noradrenalin apparently has a counterpart in their sparse vasomotor supply. This is also in keeping with the fact that the lungs, striated muscle and the brain normally contain little noradrenalin in comparison with other organs, such as the spleen, the kidneys, the salivary glands and the heart. Thus the lungs and brain contain only about 1/10–1/20 of the noradrenalin in the spleen.

It is thus apparent that the circulatory actions of noradrenalin differ in important respects from those of adrenalin. Apart from the circulatory actions, noradrenalin also differs significantly from adrenalin in some other respects. Thus the metabolic actions of adrenalin, as, for example, on total oxygen consumption, blood sugar, blood lactic acid, number of white blood cells and so forth, occur to only a small extent with noradrenalin. To obtain the same actions as with adrenalin, about five to ten times higher doses of noradrenalin are required. This has an important bearing on the question of the so-called wasteful O_2 consumption of the heart. There is good

evidence that adrenalin causes an effect of this kind, but there is little reason to suspect that this effect occurs with noradrenalin to any appreciable extent. For the therapeutic use in cases with diseased hearts this effect of adrenalin is clearly of high significance. On the other hand, it would be awkward if the organism used a tool in the blood pressure homeostatic mechanism which caused untoward effects on the heart.

Another difference of interest is that the subjective symptoms in man after noradrenalin are much weaker than after adrenalin, probably due to the weak metabolic effects on nerve structures of noradrenalin.

The effect of a chronic infusion of large amounts of noradrenalin can be conveniently studied in certain cases of pheochromocytoma, where the amounts "infused" from the tumor may be as high as 1 to 2 μg. noradrenalin per kilogram per minute, or about 5 mg. per hour [7] (figure 2). From the

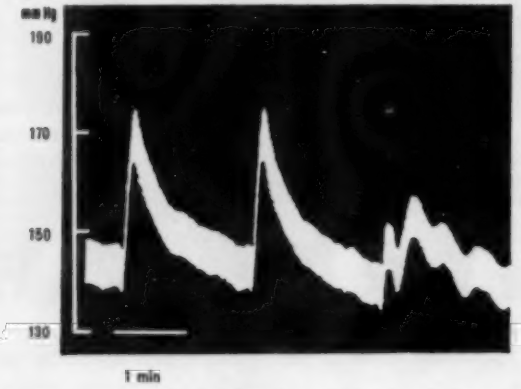

FIG. 2. Blood pressure, cat. Effect of injection of 0.1 ml. urine from a patient with pheochromocytoma, followed by 0.3 μg. noradrenalin and 0.4 μg. adrenalin.

information gained in such cases it can be concluded that chronic infusion of large doses does not lead to tachyphylaxis, the blood pressure remaining elevated as long as the tumor continues to release noradrenalin. The heart apparently suffers little damage from the continuous secretion, since it may work for years at the high pressure. Metabolic changes are usually mild, though sweating and muscular weakness may occur, probably as a result of sudden increases in the release. The subjective symptoms are as a rule not very pronounced. In fact, many cases may pass as essential hypertension, due to the unobtrusiveness of the symptoms.

If we can predict from the results of physiologic experiments and clinical experience when noradrenalin may be expected to be of therapeutic use, we may also be able to obtain information by observing the conditions under which noradrenalin is released from the nerves and the suprarenals.

The suprarenal glands of nearly all vertebrates contain noradrenalin,

though the proportion varies between a few per cent (whales) and nearly 100 per cent (rabbits) of the sum of adrenalin and noradrenalin. In a series of cases of adrenalectomy in man the fresh gland contained on an average 0.09 mg./gm. noradrenalin, corresponding to a total amount of 1 to 2 mg. It can be assumed that the noradrenalin is stored in the gland for emergency purposes, and it is of interest to note that the fetal organism has much noradrenalin in its store but very little adrenalin.[15]

It is known that the sympathetic vascular nerves are activated by deflation of the carotid sinus, as, for example, during carotid occlusion, or when the pressure drops in the aorta. Under such conditions the suprarenal glands also increase their secretion.

The release has been studied directly in experiments on cats in which the suprarenal blood has been collected and assayed. Analysis has revealed

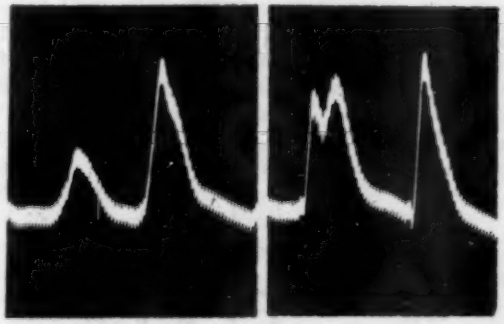

FIG. 3. Blood pressure, cat. Effects of injections of 1 ml. suprarenal venous blood from "spontaneous" secretion and during carotid artery occlusion, followed by 0.4 μg. adrenalin and 0.25 μg. noradrenalin. (From U. S. von Euler et al., Scandinav. J. Clin. and Lab. Invest. 5, 122, 1953.)

that about 75 per cent of the secretion consists of noradrenalin,[17] which is in contrast to the selective secretion of adrenalin during hypoglycemia,[4] or the high percentage of adrenalin during stressful stimuli [7] (figure 3).

Also by studying the excretion of noradrenalin in urine we may obtain information about the conditions under which it is released in the organism. Normally a small proportion of the noradrenalin produced in the body is excreted,[9] and it can be shown that this differs according to the state of activity and other factors. During night rest or in recumbent position the excretion is low but it increases during head-up position [20] or muscular work [10] (figure 4).

If the natural release of noradrenalin is prevented by ganglionic blocking agents, muscular work is accompanied by a profound fall in blood pressure.[24] It has also been shown that during postural hypotension in man the noradrenalin secretion is lower than normal.[20]

After adrenalectomy in man the adrenalin excretion is strongly reduced, while the noradrenalin excretion is unchanged or even increased.[8] Signs of circulatory insufficiency are not generally observed in patients adequately maintained on cortisone, which speaks against adrenalin's having a determinant rôle in the blood pressure homeostasis.

Since noradrenalin is the chief factor for the maintenance of the normal blood pressure and represents the emergency hormone used by the organism to raise a low pressure, it is not surprising that it should be tried in clinical situations of lowered arterial blood pressure with either unchanged or decreased flow. The use of noradrenalin in circulatory deficiency was initiated by Goldenberg et al.[13]

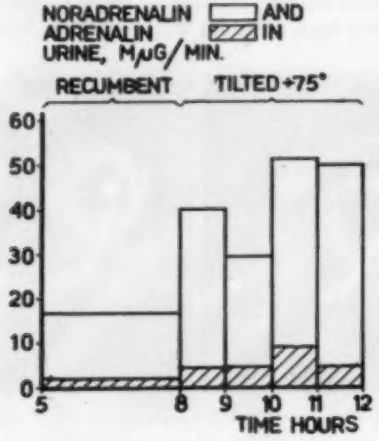

FIG. 4. Noradrenalin and adrenalin excretion in urine in normal individual during recumbent and head-up position (Sundin and Euler, 1954).

In the first condition the blood pressure homeostatic mechanism is probably functionally defective. This may be encountered in cases of lowered sympathetic tone caused, for example, by spinal anesthesia, sympathectomy, ganglionic blocking agents and drugs paralyzing the central vasomotor mechanism. Unless the blood pressure drops to low values, the condition is not serious because the flow remains adequate. On the other hand, certain functions will suffer if the pressure remains low for any length of time. In these conditions the pressure is usually readily restored with noradrenalin, which then actually serves as substitutional therapy. The rise in blood pressure is not accompanied by gross alterations in flow.

The second condition is more serious and more complex, and is encountered in certain states of shock. Noradrenalin was first used in cardiogenic shock by Kaindl and Lindner,[18] and encouraging results have been obtained by a number of authors.[21]

A sudden decrease in the pumping activity of the heart leading to decrease in both flow and pressure, such as in cardiogenic shock (myocardial infarction), may be corrected by noradrenalin which is released under these conditions and is also beneficial when administered. The favorable effect of noradrenalin is probably partly due to an improved irrigation of the damaged heart which is essential during the first critical period.

If a loss of intravasal fluid has occurred, the immediate drop in blood pressure and flow is normally compensated for to a certain limit by the blood pressure homeostatic mechanisms, involving an activation of the vasoconstrictor noradrenalin producing system. Only if this is exhausted, or else ineffective, may exogenous noradrenalin be expected to assist in raising the blood pressure by reducing the volume of the vascular tree and by increasing the resistance.

The usefulness of noradrenalin in such conditions may be inferred from the fact that it is normally released in these situations not only by the adrenergic nerves but also by the suprarenals.

In the first stages of shock, vasoconstriction is generally encountered and should be expected. However, there is often a tendency for the vasomotor response to become less efficient with time, and in such conditions infusion of noradrenalin might help to maintain vascular tone. A drug which tends to dilate the muscle vessels like adrenalin is less appropriate for the purpose of safeguarding the flow in important organs. It is clear that the condition outlined above would be more easily dealt with if the fluid loss is compensated for by infusion of blood or a plasma expander. However, the circumstances are not always such as to allow a rapid and adequate substitution of fluid. Even restitution of the blood volume may not always be effective in raising the blood pressure, as is frequently observed. Noradrenalin may then serve as a pharmacologic crutch—to use the fitting expression of Tainter—during a critical period.

By using isotope labeled red blood cells, Nylin and Pannier [22] have shown that mixing may be very slow in circulatory insufficiency, indicating pooling of blood.

Obviously the effectiveness of noradrenalin in restoring a low blood pressure is dependent upon the responsiveness of the vessels. Unfortunately, this may deteriorate gradually during states of prolonged low pressure and inadequate flow. The reasons for this may be manifold: toxic products, anoxia, lack of conditioning or permissive factors like cortical hormones have to be taken into consideration. Under such conditions noradrenalin may be inefficient, but this would probably apply to all drugs of this kind. It is therefore of paramount importance that the therapy be instituted at a time when the vessels still react.

The intense vasoconstrictor action of noradrenalin has also prompted its use as an adjuvant in local anesthesia. In this respect it is almost as active as adrenalin but possesses certain advantages in that it causes

almost none of the disturbing side actions of adrenalin, such as tachycardia, apprehension and irritability.

In spinal anesthesia it is possible to prolong the duration of the anesthesia by about 100 per cent if 0.5 mg. noradrenalin is added to the analgesic drug. This effect is due to vasoconstriction in conjunction with slow resorption, and it is not followed by any untoward actions as judged by the experience from 1,000 cases [19] (figure 5).

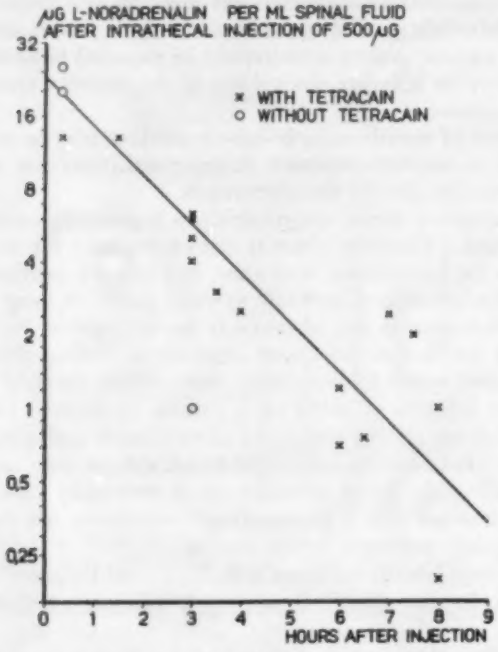

FIG. 5. Noradrenalin in µg./ml. spinal fluid, different times, after intrathecal injection of 0.5 mg. with and without Pontocaine in man. (From S.-O. Liljedahl and U. S. von Euler, Acta Chir. Scand., in press.)

Summarizing, we may say that the explanation of the beneficial effects of noradrenalin in many conditions is still incomplete, partly owing to our unsatisfactory knowledge of circulation during hypotensional states. Noradrenalin is not a panacea which can be expected to give striking results in all kinds of hypotension. On the other hand, it represents a safe and efficient means of restoring a falling blood pressure in many situations where the low pressure is a vital indication, and the release from the natural sources is insufficient.

RENAL FUNCTION IN CONGESTIVE HEART FAILURE *

By W. B. Youmans, M.D., Ph.D., *Madison, Wisconsin*

To emphasize the renal problems, congestive heart failure may be defined as a condition in which there is a decrease in the ability of the kidneys to excrete sodium chloride and water, with the result that a positive salt and water balance develops in the presence of a normal or reduced intake. In this paper some of the evidence that congestive heart failure is characterized by retention of sodium chloride and water will be presented, and then studies which serve to establish the nature of the changes in renal function will be considered.

I. The Retention of Sodium Chloride and Water in Congestive Heart Failure

The fact that water is retained in the body in patients with chronic heart failure is apparent. There are dependent edema, ascites, hydrothorax, and engorgement of the lungs, the liver and the great veins. When the patient is effectively treated diuresis occurs: fluid disappears from the body cavities, and the edema and the engorgement of the liver, lungs and venous system are relieved. In a normal individual the total body water accounts for about 55 to 60 per cent of the body weight. The body water is visualized as being contained in compartments: the initial subdivision is into intracellular fluid and extracellular fluid, and the extracellular fluid is further subdivided into blood plasma and the interstitial fluid. The fluids found in the three compartments differ from each other in composition because of the differences in the permeability of the two barriers—the cell wall, which separates the intracellular fluid from the extracellular, and the capillary wall which separates the blood plasma from the interstitial fluid. In the consideration of congestive heart failure it is important to keep in mind the fact that the capillary wall allows free passage of sodium and other plasma constituents except protein, whereas the cell wall does not allow sodium to pass readily. When sodium chloride is retained in the body it is to be expected that a rise in volume of the two compartments which make up the extracellular fluid will result, while one would not expect to find any rise in the volume of the intracellular fluid. According to figures tabulated by Friedberg,[1] the anticipated result is the one which is obtained in studies of changes in fluid compartments in patients who are becoming decompensated. Plasma volume increased 40 to 50 per cent, interstitial fluid was tripled in amount,

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while intracellular fluid showed a slight decrease. An increase of 12 L. in the total body water, all of which increase was confined to the extracellular fluid compartment, accounted for the 12 kg. increase in body weight. This illustrates what occurs as a patient goes into decompensation when treatment is withheld. Myers and associates [2] quantitated the reverse changes in sodium chloride and water balance which occur during recovery from congestive failure. They found that the body weight decreases on a constant caloric intake. In a specific case a decrease in weight of 12 kg. occurred within 13 days, during which time 9 kg. more water was eliminated from the body than was ingested. The amount of sodium chloride lost in excess of that taken in during this time was about the amount required to make 10 L. of 0.9 per cent sodium chloride solution. Thus the loss of weight is shown to be accounted for by the loss of water and salt.

Another way to quantitate the reduced ability of the patient with congestive failure to excrete sodium chloride is to determine the amount of salt excreted during a given period following administration of a measured amount of salt to the patient under basal conditions. This was done by Burch and co-workers [3] using radioactive sodium, and it was demonstrated that the normal patient excretes the sodium several times as fast as the patient in congestive failure.

II. Mechanism of Renal Retention of Sodium Chloride and Water in Congestive Heart Failure

The failure of the kidney to excrete a substance theoretically may be related to any or all of three changes: (1) reduction in the amount of the substance filtered through the glomerulus; (2) increase in the amount reabsorbed by the renal tubule, or (3) reduction in amount excreted by the tubule. However, since no physiologic substances present in plasma in considerable amounts (with the exception of creatinine when the blood level is increased above normal) are removed from the plasma by tubular excretion, a substance is retained because of either reduced filtration or increased tubular reabsorption. The filtration process is passive and the rate of filtration is related mainly to the pressure in the glomerulus; tubular reabsorption, on the other hand, is a passive process with regard to some substances, such as urea, and an active process with regard to other substances, notably glucose and sodium.

A. *Renal blood flow, glomerular filtration rate and filtration fraction in patients with congestive heart failure:* The amount of renal blood flow (RBF) and the glomerular filtration rate (GFR) in patients with congestive heart failure have been studied sufficiently to establish that in the great majority of cases the values are reduced.[4, 5, 6, 7, 8, 9] Furthermore, the RBF regularly is reduced more than the GFR; therefore, the filtration fraction (FF), which is the ratio of GFR/RBF, is increased. The results reported by Newman [7] are typical. A 30 year old man with a history of rheumatic

heart disease had dyspnea and minimal cyanosis on exertion; he had definite but minimal edema of the feet and a venous pressure of 16 cm. of water. His heart was enlarged to the left and right; the left auricle was enlarged, calcification of the mitral valve was demonstrated by x-ray, and the electrocardiogram revealed auricular fibrillation. The GFR was 70 to 80 c.c./min., which was about 60 per cent of the expected normal for this patient, since he was a large man, and the renal plasma flow was 180 to 220 c.c./min., which is about 30 per cent of the normal. This gives a filtration fraction of 0.40, which is about twice normal.

Another patient in congestive failure following an old anterior myocardial infarction had a GFR of 80 to 90 c.c./min., which is two thirds of the normal value, a renal plasma flow of 200 c.c./min., which is one third normal, and a filtration fraction of 0.30 to 0.40, which is 50 to 100 per cent above the normal range. In occasional cases the GFR and RBF are equally decreased, so that the ratio (filtration fraction) is unchanged, but this is exceptional.

The changes in RBF, GFR and FF seen in congestive failure are what one might predict to occur to compensate for a decrease in cardiac output. A decrease in cardiac output leads to a fall in arterial blood pressure and, consequently, to a decrease in pressure in the renal artery and in the glomerulus. Such a fall in pressure would be associated with a decrease in both RBF and in the head of pressure available for producing the glomerular filtrate in the kidney, provided no change in resistance to flow of blood through the kidney occurred simultaneously. In fact, however, a fall in arterial pressure reflexly elicits constriction of arterioles throughout the body. In the kidney two sets of arterioles are influenced, the afferent and the efferent arterioles. It can readily be visualized that constriction of the afferent arterioles would lead to decreased RBF by imposing an increased resistance to flow, and would lead to a decrease in pressure in the glomerulus, which is downstream. An increase in efferent arteriolar tonus, on the other hand, would cause a rise in pressure in the glomerulus, which is upstream, at the same time that it reduces RBF. Thus, it may be concluded that in congestive heart failure typically there is constriction of the efferent arterioles of sufficient degree to elevate the FF. This does not mean that there may not be some degree of constriction of the afferent arterioles also, but the predominant effect is related to the efferent arteriolar constriction.

Since the cardiac output typically is not greatly reduced, or may even be within the normal range in patients with mild degrees of true congestive failure, whereas the RBF tends to be considerably reduced, the fraction of the cardiac output which flows through the kidney is considerably reduced. Thus, blood flow through other organs is maintained at the expense of the kidney.

Since in congestive heart failure the GFR is decreased and the sodium and chloride concentrations in the plasma are not increased, the load of salt filtered, which is the product of the GFR and the plasma concentration of

these substances, is decreased. A reduction in the load of sodium filtering into the renal tubules in the absence of any reduction of sodium reabsorbing activity on the part of the tubules would result in a more complete reabsorption. Normally, about 98 to 99 per cent of the sodium load is reabsorbed, and when the sodium load is decreased this would be expected to increase to approach 100 per cent. It should be recognized, however, that a decreased sodium load, in the absence of any rise in the per cent reabsorbed, would cause a corresponding decrease in the amount of sodium excreted by the kidney per unit of time. For example, a 50 per cent reduction in GFR would result in a 50 per cent reduction in excretion of sodium chloride if the renal tubules continued to reabsorb 99 per cent of the filtered load. Actually, what might be predicted is that renal tubules which have no reduction in avidity for reabsorbing sodium would take up a greater per cent of the sodium load when the load is reduced; and in acute experiments, where the GFR is reduced by partially occluding the renal artery, this is the result obtained. It is apparent that reduction in GFR *per se* contributes to decreased ability of the kidney to excrete salt unless at the same time the sodium reabsorbing activity of the renal tubules is depressed. Such a compensatory depression in renal tubular activity could occur if there was a reduction in output of the salt-retaining hormone of the adrenal cortex. Thus, it is not necessary to postulate an increased production of an adrenal cortical hormone to explain the salt retention in congestive failure; one may postulate simply that the adrenal cortex does not undergo decreased activity to permit excretion of a larger fraction of the reduced sodium load. From conditions other than congestive heart failure it is evident that the kidney is not obliged to retain salt when the GFR is reduced. Although unilateral nephrectomy, for example, will cause a considerable reduction in the patient's GFR (almost 50 per cent at first, followed by gradual recovery up to about 70 to 80 per cent of the preoperative level), no serious impairment of the ability of the individual to excrete salt such as is seen in congestive heart failure is produced. It is apparent that the decreased GFR following unilateral nephrectomy is compensated for by a decrease in sodium reabsorbing activity, so that salt is excreted about as before. If, as seems well established, one of the functions of the adrenal cortex is to regulate the amount of salt in the body, then the adrenal cortex must in some way be informed of any necessity of increasing or decreasing its output of salt-retaining hormone. Following unilateral nephrectomy the tendency would be for the salt content of the body to increase (if salt ingestion was maintained) if less were filtered and the same fraction reabsorbed, but either a rise in concentration of salt in body fluids or an alteration in either the volume or the composition of one of the fluid compartments must in some way signal the adrenal cortex to decrease its output of salt-retaining hormone, with the result that less of the filtered load is reabsorbed. The precise mechanisms by means of which the liberation of salt-retaining hormone is controlled in order to regulate the volume of the extracellular fluid are not known.

B. *Question of excess of salt-retaining hormone as a factor in congestive heart failure:* In the preceding discussion it has been emphasized that salt retention in congestive heart failure could be related simply to reduced GFR and hence reduced sodium load in the absence of any increase in the sodium reabsorbing activity of the renal tubules; however, whether such an alteration in renal tubular function occurs is a problem that can be solved only by experimentation. There have been several studies in which the urine of patients with congestive heart failure has been assayed for its ability to cause salt retention in rats.[10, 11, 12, 13] In each of these studies the urinary extract has been found to promote salt retention, while extracts prepared by similar methods from urine of patients not in congestive heart failure have had little or no salt-retaining effect. Coupled with this fact is the evidence that the adrenal cortex produces a compound which is many times as potent as desoxycorticosterone acetate in producing salt retention. The isolation of this compound was announced by Reichstein at the International Congress of Rheumatic Diseases in Geneva in August, 1953. Hamilton et al.[14] have described the results of chronic experiments on dogs in which the mitral orifice was reduced in size in several steps. Finally, a critical point was reached at which a slight additional restriction resulted in a rather sudden failure of the animal to excrete salt, and ascites developed rapidly. Adrenalectomized animals subjected to similar procedures failed to develop ascites; thus, it is suggested that the adrenal glands are necessary for the development of the fluid retention of congestive failure produced in this manner.

C. *Effects of exercise and position on renal function in congestive heart failure:* The foregoing discussion has been concerned with comparisons of renal function of patients in congestive heart failure with that of normal subjects under resting conditions. Studies concerning the effects of exercise and position on renal function have been performed in normal persons and in patients with congestive heart failure.[15, 16] A screen test for the effects of posture and exercise is to collect the 24 hour urine in two fractions, that produced during the night, and that produced while the subject is up and about. When this is done it is found that a normal person excretes more sodium chloride per hour while he is up and around than when he is recumbent. The patient with congestive heart failure, on the other hand, excretes considerably less sodium chloride per hour during the day than during the night. The congestive heart failure patient thus is developing an increasing extracellular fluid volume during the day; he is incurring a salt excretion debt which is paid in part during the period of recumbency. The ratio of the salt excretion per hour during the day to that during the night typically is equal to one or is greater in normal subjects engaged in moderate activity, while in patients with congestive heart failure it is considerably less than one. However, more data of this sort need to be accumulated to make close comparisons. The reduced salt excretion associated with the orthostatic position and exercise is not confined to patients

with congestive heart failure. It also occurs in patients with orthostatic hypotension [17] or with cirrhosis of the liver,[16] and it should be studied in patients with renal disease. It seems probable that a considerable group of conditions will lead to reduced ability of the patient to excrete sodium chloride when he is up and around.

The reduced renal excretion of salt in the patient with congestive heart failure during exercise is associated with a further decrease in renal blood flow and glomerular filtration below that found in the recumbent patient. Hence, further reduction in salt excretion during exercise may be caused by the same basic mechanisms as those contributing to salt retention in the recumbent subject.

D. *Effect of treatment on renal function in congestive heart failure:* Effective treatment of congestive heart failure results in the production of a negative salt and water balance. In individual cases this has been achieved by bed-rest alone, by digitalization alone, or by injection of mercurial diuretics alone in the absence of any reduction in the salt and water intake. In some cases the negative salt balance has been produced by these methods in the presence of an increased salt intake. When the three procedures are combined and salt ingestion is restricted, the rate of unloading of the excess salt and water from the body is maximal.

The action of mercurial diuretics seems to be exclusively renal. The ability of the renal tubules to reabsorb sodium and chloride is decreased by these agents. Hence, even though GFR remains decreased, salt and water excretion is increased, since there is less complete absorption of the filtered load. It is generally stated that the primary effect of mercurial diuretics is on the active absorption of sodium, and that the reduced absorption of chloride and water is secondary; however, there is some evidence that chloride absorption also is directly depressed. There seems to be little question that the increased excretion of water under these conditions is secondary to the increased excretion of sodium chloride.

The mechanism of production of a negative salt balance by digitalis can be studied only if the influences of the orthostatic position, exercise and mercurial diuretics are eliminated or kept constant. The studies by Seymour and co-workers,[18] Bradley and Blake,[19] Newman [7] and others [20, 21] establish that an increase in the RBF and GFR commonly occurs in patients with congestive heart failure who are treated by digitalization. Such patients also may show an increase in the cardiac output if the output is subnormal before digitalization, or the improved heart action may be manifested by the maintenance of a normal cardiac output at a lower venous pressure. The primary action of digitalis is to improve the response of the heart to the venous load; secondarily, the RBF and GFR are increased, and this would promote an increase in sodium chloride excretion if the renal tubules continue to function as before digitalization. However, it is possible that reduced production of a salt-retaining substance may also be

effected in some way by digitalization. Although the GFR is increased in most patients recovering from congestive heart failure during treatment, the increase in some cases is insignificant and in still others no increase occurs. Such results have been reported by all three groups of investigators mentioned above.[7, 18, 19] Newman, in particular, studied effects of digitalization alone and found that some cases showed an increase in sodium chloride excretion without any increase in the GFR. A decreased sodium reabsorbing activity of the tubules must have occurred in such cases. Hence it appears that the restoration of compensation by digitalis may be related in part to something more complex than simply an improved RBF and GFR, although these latter changes may play a rôle in individual cases.

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MECHANISM OF HIGH OUTPUT CIRCULATORY FAILURE*

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From time to time physicians have noted certain similarities between the syndrome produced by a systemic arteriovenous fistula and the cardiovascular effects produced by chronic thiamine deficiency.[1] Not only do the circulatory patterns in these two conditions resemble each other, but also the circulatory changes produced by therapy with large doses of thiamine in patients with beriberi heart disease are similar in several respects to those associated with closure of an arteriovenous fistula.[1] It has become common practice to refer to the circulatory failure of the type produced by beriberi and arteriovenous fistula as high output failure, in recognition of the fact that in such conditions the cardiac output is considerably above the normal range (except in the terminal phase), whereas in congestive failure produced by hypertension, myocardial infarction or cardiac valvular lesions the cardiac output is within the normal range or decreased. In addition to arteriovenous fistula and beriberi, several other conditions may lead to the high output failure syndrome. These include severe anemia, hyperthyroidism, certain types of chronic pulmonary disease, patent ductus arteriosus and Paget's disease.

I. Differentiation of High Output Failure Syndrome and True Congestive Failure

When one studies the pattern of circulatory changes in beriberi and arteriovenous fistula and in true congestive failure related primarily to weakness of the left ventricle, the similarities between arteriovenous fistula and beriberi are found to be fundamental, whereas the similarities between the high output failure syndrome and the true congestive failure syndrome are found to be related almost entirely to the fact that the volume of the extracellular fluid compartment is increased in both. If one sorts out the signs and symptoms related to increased extracellular fluid volume, the remaining deviations from the normal are strikingly different in the high output failure syndrome from those in true congestive heart failure. Since the principal difference between high output failure and true congestive failure is the elevated cardiac output, one must search for a mechanism which is promoting an increase in cardiac output in the former but not in the latter. It is possible that more than one mechanism is involved in a given disease leading to the high output failure syndrome, or that different mechan-

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isms may be concerned in the different diseases. In this discussion of high output failure I shall consider particularly (1) the basis for the increased cardiac output, and (2) the mechanism of the increase in extracellular fluid volume. Before proceeding with these problems, however, I shall summarize the similarities and differences between high output failure and true congestive failure. In both syndromes there may be venous congestion, cardiac dilatation and edema. These changes are attributable primarily to the increased extracellular fluid volume. The differences are that there are increased cardiac output, increased circulatory rate and a decreased arteriovenous oxygen difference in high output failure, whereas these change in the opposite direction or not at all in true congestive failure.[2, 3] The increased circulatory rate and the decreased arteriovenous oxygen difference are related to the increased cardiac output. Finally, in all of the diseases which lead to high output failure there is a reduced resistance to the run-off of blood from the systemic arterial tree.[3] The total resistance to flow of blood which is encountered in the systemic circuit is called the total peripheral resistance, or simply the peripheral resistance. Most of the total peripheral resistance resides in the arterioles of the systemic circuit, where the relatively viscous blood flows through very small tubes. The main bases for a decrease in the peripheral resistance are (1) shunts, which channel the blood around the resistance interposed by the arterioles; (2) dilatation of the arterioles, and (3) lowered viscosity of the blood. If we now look at the list of diseases leading to the high output failure syndrome, we can attribute the decreased peripheral resistance to shunts in the case of arteriovenous fistula, patent ductus arteriosus and Paget's disease; to arteriolar dilatation in the case of beriberi, hyperthyroidism and possibly anemia, and to lowered viscosity of the blood in the case of severe anemia. In some cases of chronic pulmonary disease a decrease in the peripheral resistance occurs in mild degree, and the mechanism may be the local vasodilator effects of lowered oxygen tension.

Whereas a reduced peripheral resistance is a common denominator in the high output failure syndrome, the peripheral resistance is increased in true congestive failure. In failure of the circulation related to weakness of the left ventricle one would expect that the peripheral resistance would be increased as a compensatory response, since any tendency toward a decreased cardiac output resulting in a fall in arterial blood pressure elicits from pressoreceptors in the carotid sinuses and aortic arch a constriction of the arterioles in the skin and splanchnic viscera, thus increasing the resistance to flow of blood through these vascular beds. The kidney is particularly sensitive to the vasoconstrictor influences which develop in patients with true congestive failure, and the reduction in renal blood flow, such as occurs in congestive failure according to some investigators, causes production of renin, and this also contributes to a generalized rise in arteriolar tonus.[4]

The primary change in the cardiovascular system which leads to the

development of the high output failure syndrome probably is the chronically decreased peripheral resistance. There are four main reasons for considering the peripheral defect as the primary one. First, in arteriovenous fistula, which may lead to the typical high output failure pattern, the initial defect is known to be peripheral. Second, decreased peripheral resistance occurs in all conditions leading to high output failure. Third, an increased cardiac output occurs as a compensatory response to low peripheral resistance. Fourth, renal retention of sodium chloride and water can be explained by the shunting of blood away from the kidney due to a disproportionate loss of resistance in the extrarenal portion of the systemic vascular bed.

II. Circulatory Adjustments in Arteriovenous Shunt

The most instructive member of the high output failure family to analyze in an attempt to understand hemodynamic changes is arteriovenous fistula. The principal reason for this is that the initial defect in the cardiovascular system is obvious. A second reason is that arteriovenous fistula can be produced experimentally, hence both the immediate and the delayed effects of establishing and of closing a fistula may be studied.

Immediate effects of arteriovenous shunt: The immediate changes due to establishment of an arteriovenous fistula of moderate size are listed by Emile Holman as follows [8]:

1. A fall in general *arterial blood pressure* affecting both diastolic and systolic levels.
2. An increase in *pulse rate.*
3. An increase in the *cardiac output.*
4. An *increase in the pressure in the involved vein,* proximal and distal to the fistula.
5. A *decrease in the size of the heart.*

To this list may be added the observation, made by several groups of investigators, that the central venous pressure or right atrial pressure is not increased and in fact may be slightly decreased immediately following the establishment of an arteriovenous shunt.[6, 7, 8] One might, at first consideration, visualize that a more rapid run-off of blood from the arteries to the veins would increase right atrial pressure at the same time that it lowers arterial blood pressure. However, the pressure becomes increased in the entire venous bed peripheral to the site of the shunt, and such a rise in pressure cannot occur without a loss of blood into that venous and capillary bed. Thus, when a shunt is opened the animal bleeds into the involved venous bed, and the effect on the central venous pressure is not unlike that which would be produced if a vein were obstructed with a cuff creating a pressure of around 60 to 70 mm. of Hg. The pressure and volume of blood in the part are increased, the central venous pressure is lowered and the diastolic heart size decreases.

There is a second mechanism for the decrease in right atrial pressure and in the size of the heart immediately following the opening of an arteriovenous fistula. The fall in arterial blood pressure reflexly, as a result of the lowered pressure in the sino-aortic pressoreceptive zones, causes stimulation of the heart through its sympathetic nerves, and at the same time vagal tonus is depressed.[9] An increased heart rate occurs and cardiac output is increased. The rise in cardiac output elicited in this way contributes to a lowering of the venous pressure and counteracts to some extent the fall in arterial blood pressure which is produced by the lowered peripheral resistance.

Immediately following the establishment of an arteriovenous shunt in experimental animals the arterioles of the systemic circuit undergo active constriction.[6] This also is a reflex response elicited by the fall in pressure in the sino-aortic pressoreceptors. It serves to counteract the fall in arterial blood pressure, but it has the detrimental effect of decreasing the flow through the organs of the body and increasing the flow through the shunt. The vasoconstriction begins to wear off shortly, possibly because of the local vasodilator effects of lowered oxygen tension, increased carbon dioxide tension and increased hydrogen ion concentration secondary to the decreased blood flow.

Delayed effects of arteriovenous shunt: The circulatory pattern immediately following production of an arteriovenous shunt is quite unlike that seen weeks or months later. In fact, in the acute phase, as stated by Holman,[5] there is a resemblance to massive hemorrhage (decreased arterial pressure, vasoconstriction, decreased right atrial pressure, reduced heart size, etc.), and at this stage transfusion would indeed be expected to be beneficial.

The delayed effects of arteriovenous shunt on the general circulation are:

1. An *increase in blood volume* of a degree which is roughly correlated with the size of the fistula.
2. *Elevation of the venous pressure* to levels well above the normal range.
3. *Enlargement of the heart* which, according to Holman,[5] "is due mainly to dilatation and only to a minor degree to hypertrophy."
4. "A gradual recovery from the lowered blood pressure noted immediately after the formation of the fistula, the systolic being equal or higher, the diastolic definitely lower than existing before the formation of the fistula, thus producing a *greatly increased pulse pressure.*"
5. The *heart rate continues to be fast.*
6. The *cardiac output remains elevated.*
7. Finally, *vasoconstriction is not a part of the picture* in chronic arteriovenous shunt.

How can one best explain the shift from the circulatory pattern seen in the acute stage to that seen weeks, months or years later? It is probable that the basic change is the gradual rise in blood volume. This would con-

tribute to a rise in central venous pressure, better cardiac filling, a further increase in cardiac output above that seen in the acute stage, and a restoration of the mean arterial blood pressure.

The fact of the rise in blood volume in chronic arteriovenous shunt is well established.[5, 8, 10, 11] The basis and the mechanism for the rise could be identical to that for the rise in blood volume and extracellular fluid volume seen in true congestive failure. In the case of true congestive failure it appears that failure of the heart to pump a normal amount of blood at a normal venous pressure causes a retention of sodium chloride and water in the body until a venous pressure level is reached that stimulates the weak heart to pump a normal amount of blood. In arteriovenous shunt the blood which passes across the shunt serves no useful purpose; and, initially, the amount of blood which flows through the capillary beds of the systemic circuit is decreased in amount just as it is in true congestive failure. Hence, if a decrease in the blood supply to some organ is the important factor in initiating sodium chloride and water retention in the presence of a decreased cardiac output, the same change should result from an arteriovenous shunt. The immediate effect of an arteriovenous shunt is to cause a decrease in the flow of blood through the kidney and a decrease in the head of pressure available for production of glomerular filtrate. The amount of sodium chloride filtered is lowered. If there is no corresponding reduction in the rate of reabsorption of sodium chloride by the renal tubules, salt and water will be retained in the body. The studies by Bobb, Lillehei and Visscher indicate that dogs with arteriovenous fistulas have a reduced ability to excrete sodium chloride.[12] The retention of salt might be self-limiting if, through this device, the venous pressure is raised and the cardiac output increased until renal blood flow and glomerular filtration rate are restored. In such a case the high output failure syndrome might be maintained unchanged for a prolonged period. On the other hand, if the severity of the conditions was such that renal blood flow and glomerular filtration rate (or blood flow to some other organ which is in some way responsible for the salt retention) could not be restored no matter how much the venous pressure should increase, the venous pressure would steadily rise until overdilatation of the heart would result in an acute decrease in cardiac output and acute pulmonary edema. Hilton et al. have reported a decrease in renal plasma flow, a slight decrease in glomerular filtration rate and a severe decrease in urine volume and sodium excretion during a 30 minute period that an arteriovenous fistula was open.[13]

Effect of closing an arteriovenous shunt: The changes observed on closing an arteriovenous shunt also must be subdivided into those which occur immediately and those which occur gradually. When an arteriovenous fistula is suddenly closed the well known Branham's sign is elicited.[5] This consists of a sharp rise in blood pressure and a decrease in heart rate. The rise in peripheral resistance produced by closing the shunt decreases the rate of run-off of blood from the systemic arterial tree causing a rise in

pressure, and the decrease in heart rate is elicited reflexly from the rise in pressure in the sino-aortic zones. The pressoreceptors adapt rather rapidly, so that the maximal decrease in heart rate is seen very shortly after the occlusion of the fistula, and then the rate returns toward the normal range. The sudden closure of a large shunt is recognized to be dangerous. This probably is related to the fact that the blood volume is above the normal range. It has been observed repeatedly that immediately following surgical closure of an arteriovenous shunt in a patient with cardiac dilatation, the heart size may become further increased.[14] This increase in heart size could be attributed to further weakening of a weak heart as a result of surgery; however, such an explanation is not necessary. There is a mechanical basis for the dilatation. Just as the central venous pressure falls immediately on establishing an arteriovenous shunt because the volume of blood increases in the vascular bed peripheral to the shunt, when an arteriovenous shunt is closed blood drains out of the bed peripheral to the shunt, reducing the volume in the part and increasing the volume and pressure in the great veins and in the cardiac chambers. It seems apparent that, immediately following the closure of a shunt, the patient may be in danger because of the high blood volume if his heart is already near the point of showing a decreased output in response to any further elevation in venous pressure; and once this point is exceeded a vicious cycle develops, because a decrease in the cardiac output contributes to a further rise in venous pressure.

Diuresis and development of a negative salt balance following closure of an arteriovenous shunt have been observed.[5] Within a short time the blood volume decreases to reach the normal range. In human subjects the change in blood volume observed is the amount following surgery as compared with the level before surgery.[11] According to Epstein, Post and McDowell,[15] occlusion of an established arteriovenous fistula in patients results in an increased renal excretion of sodium despite no significant change in glomerular filtration rate, renal blood or renal venous pressure. The latter values were found to be in the normal range in most cases with established arteriovenous fistula, and were not altered significantly by surgical repair of the fistula; however, none of the patients studied showed signs or symptoms of congestive heart failure. They suggest that renal excretion of sodium may be conditioned by the degree of filling of the arterial tree. It appears that the mechanism of unloading the excess extracellular fluid on occluding an arteriovenous fistula may not be simply the reverse of the mechanism for the retention of salt and water produced by opening a fistula.

Before leaving the subject of arteriovenous shunt, the rapidity of recovery which is seen even in severe cases following closure of the shunt should be mentioned. Cardiac weakness does not appear to be a factor in such cases. The heart in patients with arteriovenous fistula probably is responding as a normal heart would respond to a lowered peripheral resistance and an increased venous load. The syndrome is one which con-

ceivably could develop from a lowered peripheral resistance in the absence of any cardiac weakness. However, in individual cases which are severe and longstanding, cardiac weakness would be expected to become a complicating factor.

III. Circulatory Adjustments in Beriberi

The pattern of cardiovascular changes seen in "beriberi heart disease" is the typical high output failure syndrome.[16, 17] The signs and symptoms which develop secondary to a rise in the extracellular fluid volume may be present in extreme degree. The cardiac output at the same time may be markedly elevated. The heart rate is fast, the pulse pressure increased, evidences of vasodilatation are present and the peripheral resistance is decreased. In the terminal stages of beriberi heart disease the cardiac output decreases acutely, the blood pressure falls, the pulse pressure decreases, and acute pulmonary edema develops.

The nature of the basic circulatory defect in beriberi has been a riddle, and several possible mechanisms have been suggested. From time to time vasodilatation has been included in the list of possible bases for the beriberi heart syndrome, and there are a number of reasons to believe that this is the initial defect in the circulation in chronic thiamine deficiency which leads to the final pattern. To accept vasodilatation as the primary defect is, in effect, accepting the similarities between arteriovenous fistula and beriberi heart disease as fundamental.

Whereas an arteriovenous shunt will serve to decrease blood flow through the capillary beds of the systemic circuit, vasodilatation may cause an increase in flow through at least some of the capillary beds if venous return is maintained. The effects of acute generalized vasodilatation upon the circulation are greatly influenced by posture. In a person in the recumbent or the Trendelenburg position, where the effect of gravity is to promote venous return, vasodilator agents may cause an increase in the cardiac output. If the patient is in the upright position the well known orthostatic hypotension picture develops, a part of which is a decrease in cardiac output secondary to failure of the venous return. The total peripheral resistance resides mainly in the arterioles. Some of these arterioles normally are under a rather high degree of vasoconstrictor influence, notably those of the skin and those of the splanchnic viscera in a person in the standing position. The arterioles of the kidney, on the other hand, normally are under a low degree of vasoconstrictor influence. This is evident from the fact that 20 to 25 per cent of the cardiac output flows through the kidneys in the normal subject in the recumbent position. Since there is a high resistance normally in extrarenal vascular beds and a low resistance in the kidney, when a vasodilator agent is injected it causes a considerable lowering of resistance in extrarenal arterioles and a lesser decrease in resistance in arterioles in the kidney. This has the effect of diverting blood away from

the kidney, and hence acts, as far as renal circulation is concerned, in the same way as an arteriovenous shunt. Thus, generalized vasodilatation would be expected to cause a decreased renal blood flow and glomerular filtration rate in the recumbent subject, and the orthostatic position would contribute to a further decrease.

In beriberi heart disease the amount of blood available for the heart to pump is greater than normal. The venous pressure is increased, and this may be attributed in large part to the increased extracellular fluid volume and blood volume. The main influence upon the heart which is stimulating it to increase its output is the increased venous load. The increase in heart rate is a change which must be attributed to effects over extrinsic nerves, and it can be related to either the Bainbridge reflex or to any tendency for the mean arterial pressure to fall below normal as a result of the vasodilatation.

What is the mechanism of the rise in blood volume in beriberi? In the case of arteriovenous shunt the rise in blood volume may be postulated to be secondary to decreased renal blood flow and glomerular filtration rate. Do similar changes in renal function occur in beriberi? Only a few cases have been studied. These had a decreased renal blood flow and glomerular filtration rate in spite of the fact that the cardiac output was above normal.[18]

The therapy of a disease caused by a deficiency of thiamine, obviously, is the administration of thiamine. Less obvious are the answers to the question of how fast to relieve the deficiency and what other measures to employ. Just as the sudden closure of an arteriovenous fistula may cause further enlargement of the heart and may precipitate acute pulmonary edema, rapid administration of thiamine commonly causes a further enlargement of the heart for a few days in a patient with beriberi heart disease. One would not think of giving a large dose of a vasoconstrictor agent to a patient with pulmonary congestion, yet this appears to be the effect that thiamine has in patients with beriberi heart disease. There are two precautions: the thiamine deficiency may be relieved gradually, or the tendency to impound more blood in the lungs may be counteracted by bleeding the patient.

Are all of the conditions which lead to the high output failure syndrome to be included under the same species; or, more specifically, is a chronically lowered peripheral resistance the initial defect in each case? To answer this question each individual disease, other than the shunts, must be analyzed separately. Low peripheral resistance is a factor in each and contributes to the production of a pattern which could be called the chronically low peripheral resistance syndrome. In anemia, chronic pulmonary disease and hyperthyroidism other factors are present also, and the influences of these factors are superimposed upon the changes related to the decreased peripheral resistance. According to the recent studies of Davies and Kilpatrick,[19] the renal blood flow and glomerular filtration rate are reduced in patients with high output failure due to chronic cor pulmonale. The glomerular filtration rates of 10 patients averaged 76 c.c. per minute, while the average

for normals was 145 c.c. per minute. The average renal blood flow was about one-half of the normal level, and the range was 150 to 921 c.c. per minute. When the renal blood flow in the high output failure patients was expressed as the per cent of the cardiac output, the range was 2.0 to 15 per cent, with an average of 7 per cent, as compared with an average of 22 per cent in normal subjects. Thus it appears that the kidneys not only do not share in the increased circulation in high output failure, but the renal blood flow actually is decreased. This indicates that the extrarenal fraction of the peripheral resistance is disproportionately low, just as it is in arteriovenous shunt.

Conclusion

Each of the conditions leading to high output failure may be considered as a species of arteriovenous shunt in that there is reduced resistance to run-off of blood from the systemic arterial tree. The low peripheral resistance itself appears to be sufficient to cause the development of the syndrome. Whether there is also a cardiac weakness factor remains to be demonstrated in individual cases. If and when left ventricular weakness develops, this would be expected to contribute to a further rise in the volume of the extracellular fluid compartment and a reduction in cardiac output from the preëxisting high level.

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HORMONAL FACTORS IN HEART DISEASE: THEIR ROLE IN MYOCARDIAL HYPERTROPHY, HYPOXIA AND ELECTROLYTE IMBALANCE *

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THREE cardinal features of cardiac pathology—myocardial hypertrophy, myocardial structural degeneration and myocardial functional weakness—are by tradition ascribed to primarily mechanical factors, namely, increased hemodynamic resistance or decreased coronary blood flow or both. The inadequacy of such oversimplification is becoming increasingly obvious in the light of our growing comprehension of underlying myocardial metabolic anomalies, especially those induced or enhanced by the action of neurohormones (adreno-sympathogenic catecholamines) and hormones (adrenal mineralo-corticoids and thyroid hormone).

1. The phenomenon of cardiac hypertrophy depends to a much lesser extent on the mechanical "burden" of increased peripheral resistance than is generally believed. This is exemplified by the syndrome of "idiopathic cardiac hypertrophy", which develops in the face of a consistently normal blood pressure, by the sometimes huge hearts of normotensive acromegalic individuals, and by the frequently striking lack of quantitative correlation between the blood pressure level and the degree of cardiac hypertrophy in hypertensive patients. On the other hand, cardiac hypertrophy fails to occur despite experimentally increased vascular resistance (ligation of the aorta) after hypophysectomy, but it makes its appearance if pituitary growth hormone is administered,[1] even in animals with subnormal peripheral resistance.[2] The thyroid hormone [3] and the intracellularly sodium-depositing adrenal mineralo-corticoids [4, 5, 6] seem to sensitize the heart muscle to the hypertrophy-producing effect of the growth hormone. Thus, cardiac hypertrophy presents itself as a complex metabolic process under the leading influence of the pituitary growth hormone, apparently enhanced by the action of other hormones on cell oxidations and electrolyte balance.

2. Hypoxic myocardial degeneration and necrosis are frequently found in areas supplied by anatomically intact coronary vessels.[7, 8, 9] The popular but unproved auxiliary hypothesis of coronary spasms as a causative factor can be discarded if the powerful oxygen-wasting and hypoxia-producing metabolic effect [10, 11, 12] of the ever-present adreno-sympathogenic catecholamines, norepinephrine and epinephrine, in the myocardium is taken into

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consideration, a fundamental feature long known to physiologists but still unfamiliar to most clinicians.

The cardiac catecholamines consist predominantly of norepinephrine, discharged by the postganglionic sympathetic nerve endings,[13, 14, 15, 16, 17] and, to a lesser extent, of epinephrine, probably originating in the adrenal medulla and reaching the heart via the blood stream. Both cause a markedly intensified oxygen consumption by the heart muscle, which by far exceeds the oxygen requirements of simultaneous cardiac work.[10, 11, 12] Thus they are apt to exhaust the "coronary reserve" to the degree of "catastrophic" necrotizing myocardial anoxia,[11] especially if oxygen-conserving vagal counteraction [18] is inadequate or if the coronary vessels are sclerotic and incapable of compensatory dilatation. Catechol-induced myocardial necroses have been observed after injection of epinephrine,[19, 20, 21] after electric stimulation [22] which elicits discharges of norepinephrine into the myocardium,[17] and after intensive exercise which greatly augments the accumulation of catecholamines in the heart muscle.[23, 24]

The thyroid hormone potentiates the oxygen-wasting catechol action upon the heart muscle [25] and its cardiac toxicity,[26] probably through aminoxidase inhibition.[27]

The oxygen-consuming capacity of epinephrine has been found to be about 10 times greater than that of norepinephrine.[28, 29] Acute hypoxiating discharges of both catecholamines, if coinciding with inadequate coronary dilatability or with a possibly inadequate cholinergic counter-regulation, are believed by the writer to constitute the basic mechanism of attacks of angina pectoris.[54] Sir Thomas Lewis' hypothetic pain-producing "substance P" [30] is probably identical with unoxidized lactic acid, which accumulates in the myocardial cells under the hypoxiating influence of catecholamines.[31]

Rational and effective long-range treatment of angina pectoris accordingly consists of procedures which inhibit sympathetic neurosecretion (sympathectomy) and adrenal medullary discharges (x-ray irradiation of adrenal glands), or which desensitize the heart muscle to the hypoxiating catecholamine action (thyroidectomy, thiourea compounds, radioiodine).[54] Sympatholytic drugs are relatively ineffective, as they fail to inactivate the intrinsic myocardial catecholamines.[17]

The abnormally high epinephrine concentrations found in the heart muscle of people who have died from fresh myocardial infarctions [17] suggest that toxic action of catechols on the heart also plays a part in the events which follow such fateful episodes.

The findings of modern cardiac biochemistry make the adreno-sympathogenic catecholamines norepinephrine and epinephrine appear as agents with exquisite hypoxia-producing and consequently cardiotoxic properties, conducive to acutely painful as well as chronically destructive, necrotizing alterations of myocardial metabolism.

The customary terms "coronary insufficiency" and "coronary disease," although partially appropriate, disregard the metabolic pathogenic factors

involved. Their general indiscriminate use tends to perpetuate current non-biochemical thinking and one-sided overemphasis of purely anatomic and hemodynamic mechanisms in angina pectoris and hypoxic myocardial degeneration. "Angiometabolic hypoxia" is suggested as a clumsy but less prejudicial substitute.

3. Myocardial functional weakness of the type, leading to congestive heart failure, is characterized by (a) an inefficient cardiac oxygen economy with wasteful, relatively (in terms of cardiac work) or absolutely excessive oxygen uptake;[32, 33, 34] and by (b) a distorted myocardial electrolyte equilibrium (increased Na^+, decreased K^+).[35, 36]

(a) The first-named factor is strongly reminiscent of the metabolic effects of the adrenosympathogenic catecholamines on the heart muscle (see above). Indirect evidence in favor of a participation of metabolic catecholamine overactivity in certain forms of congestive heart failure can be gathered from various experimental and clinical observations: the production of acute left ventricular failure and pulmonary edema through injection of epinephrine, which is followed by an excessive accumulation of epinephrine in the heart muscle;[17, 37] the tendency toward congestive heart failure in uremia and in thiamine deficiency, both of which are associated with abnormal catecholamine accumulations in the myocardium;[15, 38, 39] the presence of abnormally large epinephrine concentrations in the heart muscle of patients who died in congestive heart failure;[17] the analogies of epinephrine-induced alterations of the intermediate myocardial metabolism[31, 40, 41, 42] with those detected post mortem in cases of congestive failure, such as depletion of creatine and phosphorus.[43, 44, 45] Moreover, sympathectomy,[46, 47, 48] which reduces the myocardial catecholamine content,[15, 49] and catechol-inactivating antithyroid procedures[50, 51] have proved therapeutically effective in patients with congestive heart failure. Digitalis glycosides, through their ameliorating influence upon myocardial oxygen economy,[32, 33, 34, 52] seem to counteract directly the detrimental metabolic effect of the oxygen-wasting catecholamines, without, however, possessing any other qualities of the specific "sympatholytic" drugs.

(b) The electrolyte situation in failing human heart muscles (increased Na^+, decreased K^+),[35, 36, 45] as revealed by postmortem analyses, shows analogies to the intracellularly Na^+-depositing and K^+-depleting action of adrenal mineralo-corticoids (DCA),[6, 53] whose potential effect in producing congestive failure is well known. The latter seems to be prominently involved in the congestive failure which occurs in patients with adrenal cortical tumors[54] and with toxemia of pregnancy,[54] while its rôle in the more common types of congestive heart failure is still controversial.[55, 56, 57] Findings of a diminished Na^+ concentration in the thermal sweat[58, 59] and saliva[60] of patients with congestive failure, although suggestive of adrenal cortical overfunction in this syndrome, leave unanswered the question whether such an overfunction, if present, has to be regarded as a primary causative factor

or merely as a secondary, though aggravating, stress phenomenon. Its contribution to the renal sodium and water retention [61, 62] and resulting hypervolemia in congestive failure requires further study.

The most impressive argument in favor of an at least "permissive" significance of adrenal cortical activity in retaining sodium and water in congestive failure is supplied by the often dramatic therapeutic effectiveness of total or subtotal adrenalectomy in severe, otherwise intractable cases.[63, 64] Dietary restriction of sodium seems to act in a similar fashion. Recent investigations of German, Italian and American workers [65, 66, 67] place emphasis on the intra-extracellular cation gradient and its influence on electric cell membrane potentials as fundamental factors in muscular and especially in myocardial contractility. Their findings seem to lend added weight to the concept [36] that digitalis, by restoring to normal the distorted electrolyte equilibrium of the failing human heart, improves its contractile power.

It can hardly be considered a mere coincidence that combined sympathectomy and adrenalectomy, which free the heart muscle from the "chemical burden" of both hypoxia-producing catechols and sodium-depositing, potassium-depleting corticoids, have produced particularly gratifying results in patients with severe congestive heart failure.[64]

In summarizing, it can be stated that myocardial weakness leading to congestive failure seems to be caused largely and jointly by the detrimental interference of exaggerated adreno-sympathogenic catecholamine action in myocardial oxidative energy economy, and by the distorting influence of adrenal mineralo-corticoids on myocardial electrolyte balance (increase of intracellular Na^+, decrease of K^+). Both factors are probably closely connected with each other regarding myocardial energy production (carbohydrate and phosphate metabolism), membrane potentials and depolarization, actomyosin contractility. Elimination of both catechol and corticoid effects by surgical measures proved dramatically effective in otherwise intractable cases of congestive heart failure. Digitalis, on the other hand, appears to exert its beneficial influence by correcting the cardiac metabolic effects of both catecholamine and mineralo-corticoid overactivity.

Even though the mechanistic era of functional cardiology has made tremendous and lasting contributions to our present-day knowledge, some of its most widely accepted teachings can no longer be accepted without reservation. The fortified walls of cardiology as a clinical specialty are crumbling, and more future progress can be expected from a far-flung coordination with other fields, such as endocrinology, biochemistry and biophysics, than from adherence to traditional isolationism.

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THE MEDICAL TREATMENT OF ESOPHAGEAL OBSTRUCTION *

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Since many people come to the Southwest because of chronic health problems, it is not surprising that esophageal disease is seen in this area more frequently than is ordinarily the case. The cardinal symptom of malfunction of this organ is dysphagia, and this often indicates some type of obstructing lesion of the esophagus. The purpose of this paper is to review the various types of esophageal disease which may produce obstruction, and the diverse methods of treatment which may be employed. In table 1 are listed the conditions which may produce dysphagia in varying degree. The

Table I

Diseases Causing Esophageal Dysphagia

1. Congenital abnormalities
   a. Absence
   b. Atresia
   c. Broncho-esophageal fistula
   d. Congenital webs
2. Stenosis following caustics
3. Stenosis following infection
   a. Nonspecific
   b. Diphtheria
   c. Typhoid fever
   d. Scarlet fever
   e. Tuberculosis
   f. Agranulocytosis
   g. Syphilis
4. Esophagitis due to deficiency disease
   a. Plummer-Vinson syndrome
   b. Pellagra
   c. Tetany
5. Foreign bodies
6. Collagen disease
   a. Scleroderma
7. Animal parasites
   a. Ascaris
8. Regurgitation esophagitis
   a. With hiatus hernia
   b. Following surgical procedures
9. The contraction ring of Ingelfinger
10. Stenosis following peptic ulceration
11. Idiopathic cardiospasm (achalasia)
12. Extrinsic pressure
   a. Pulsion diverticula
   b. Extrinsic tumors
   c. Deformities of the spine
13. Neoplasms

more important of these from the standpoint of the practicing gastroenterologist will be discussed.

Congenital abnormalities are the problem, chiefly, of the pediatrician and the surgeon. The increasing frequency of their successful management is a great tribute to the advances being made in these specialties.

Caustics still are an important cause of esophageal stenosis in children and following attempted suicide, but proper marking of containers as required by law has done much to reduce the incidence of this condition.

Diphtheria, scarlet fever and typhoid fever are mentioned frequently in the older literature as causes of fibrotic stenosis, but modern preventive and therapeutic measures have largely eliminated them as a problem.

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From the Veterans Administration Hospital, Tucson, Arizona.

Of the deficiency diseases the Plummer-Vinson syndrome, with its glossitis, anemia and dysphagia, is the classic example, although pellagra also may produce esophagitis and obstructive symptoms.

Foreign bodies occur not only in the very young but also commonly in people with large dentures who, for this reason, have lost much of their normal buccal discrimination. Individuals with dental plates should be extremely careful about placing pins or other foreign bodies in the mouth, and in masticating foods which may contain bone or other foreign bodies.

Collagen diseases, notably scleroderma, may produce a particularly distressing form of dysphagia and one difficult to benefit.

Obstruction of the esophagus from coiled collections of ascaris have been reported in children, but apparently this is quite rare.

Regurgitation esophagitis with spasm or stricture is seen commonly as a cause of dysphagia. The basic pathology in this condition results from the prolonged irritation of the mucosa of the distal esophagus by regurgitation of gastric contents, with resultant esophagitis, spasm, ulceration and stricture formation as the ultimate situation which may occur. A prerequisite for its development is, ordinarily, a disturbance of the mechanical relationship of the distal esophagus to the cardia of the stomach. Such disturbance is most commonly produced by a hiatus hernia, but also is seen frequently after surgical intervention either for cardiospasm when a plastic procedure is done, or for tumor or stenosis when a resection has been performed. Regurgitation esophagitis also occurs occasionally with pregnancy and in diseases requiring prolonged bed-rest. Rarely it is present without any obvious cause. It should be noted that while hiatus herniation of the congenital type may lead to esophagitis, fibrous esophagitis may in other cases be the primary event and, by causing esophageal shortening, may produce hiatus herniation.

Case Reports

Case 1. In the x-ray (figure 1) of this case a small hiatus hernia is seen. There is no evident stricture formation, but this patient has recurring troublesome obstructive manifestations which require periodic dilatation. These episodes frequently follow dietary indiscretions. Improperly chewed meat is usually the obstructing agent. Since the patient lives some distance from Tucson, he has been taught to dilate the esophagus himself with a soft mercury-filled bougie.

Case 2. This patient, a minister, developed a traumatic hiatus hernia following unaccustomed exertion. As seen in the x-ray (figure 2), ultimately stricture formation and marked secondary shortening have developed. The resultant persistent and progressive dysphagia has been relieved satisfactorily for a 12 month period by dilatation by means, initially of olives over a string, and then by a mercury bougie.

Case 3. This case illustrates the stricture formation which may result from regurgitation esophagitis secondary to a hiatus hernia, probably of the short esophagus type (figure 3). This patient has been relieved of obstructive symptoms for a period of two years by means of dilatation with, initially, olives over a string, and then a mercury bougie.

FIG. 1. *Case 1.* Hiatus hernia with recurring obstructive manifestations. No gross evidence of regurgitation esophagitis is present.

The contraction ring of Ingelfinger consists of a contraction ring in the distal esophagus which produces varying degrees of obstruction. Typically, it is seen to disappear when the esophagus empties, and it may shift its position to some extent.

Primary peptic ulcer of the esophagus developing on a basis of aberrant gastric tissue is rare. Esophageal ulceration usually is secondary to regurgitation esophagitis or neoplasm.

Cardiospasm or achalasia is one of the more common causes for dysphagia seen in this section of the country. It is caused by a nonorganic neuromuscular dysfunction of the esophagus, manifested by impaired peristalsis of the organ as a whole and by a failure of the cardia to open when stimulated by ingested contents but not by retained contents. The difficulty in swallowing which results is unique in that it is commonly more difficult to swallow liquids than solids. Of importance also is the fact that frequently the initial and only symptom for long periods is cough due

to nocturnal spillage of mucus into the tracheobronchial tree. Some of these patients are treated for chronic bronchitis for extended periods before the true nature of the difficulty is discovered. The following cases illustrate some of the variations manifested by this disease.

Case 4. This 20 year old girl has had symptoms for four years, and the x-ray (figure 4) illustrates the anatomically less advanced type of cardiospasm. There are only moderate dilatation and retention of barium, with little evident mucus and no tortuosity or retention of food. This patient elected surgical treatment and, while relieved of dysphagia, has had recurring episodes of painful regurgitation esophagitis during the subsequent three year period.

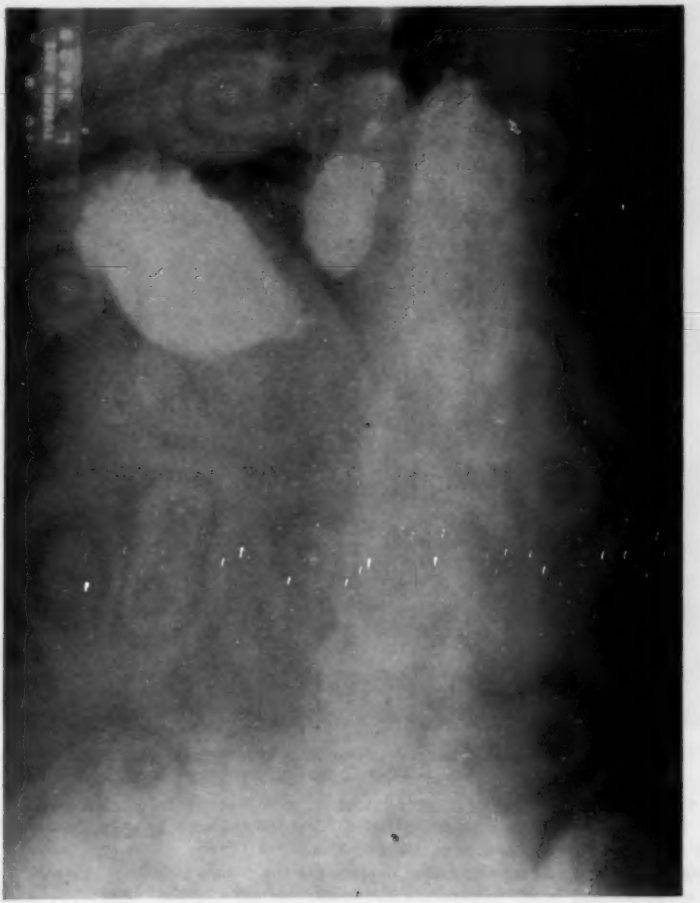

FIG. 2. *Case 2.* Traumatic hiatus herniation. Above the pouch a segment of the terminal esophagus has stenosed, producing symptoms of obstruction.

Case 5. A 42 year old male with idiopathic cardiospasm on x-ray (figure 5) shows more dilatation than in the preceding case and there is greater obstruction to the passage of barium. There is beginning tortuosity, and large amounts of mucus are evident. This patient has been asymptomatic for 24 months following hydrostatic dilatation.

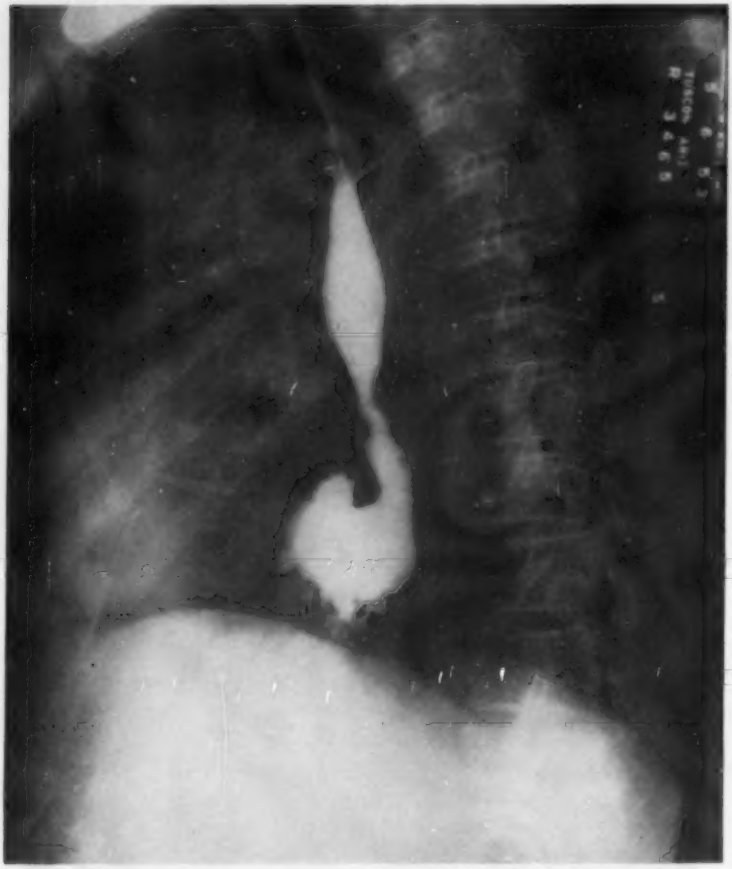

FIG. 3. *Case 3.* Stricture formation resulting from regurgitation esophagitis secondary to hiatus hernia, probably of the short esophagus type.

Case 6. This 86 year old male is the oldest patient seen by us with cardiospasm. The x-ray (figure 6) indicates marked dilatation of the esophagus, with a large amount of mucus and a large filling defect near the cardia produced by retained food. This patient has been relieved of symptoms for 18 months following hydrostatic dilatation.

Extrinsic pressure may result from abscesses, granuloma, neoplasm or large pulsion diverticula of the pharynx or epiphrenic regions. In the Tucson area, however, they chiefly result from the distortions which occasionally are produced by mutilating intrathoracic procedures, usually in

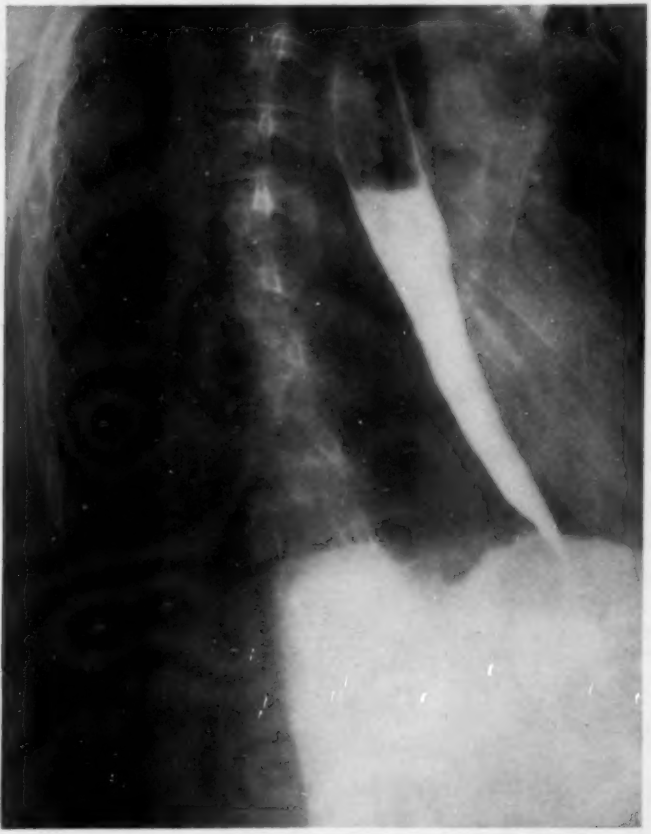

FIG. 4. *Case 4.* Idiopathic cardiospasm of four years' duration in a girl of 20.

tuberculous individuals. Tuberculosis also may produce an esophagobronchial fistula as the result of a tuberculous mediastinal lymph node eroding simultaneously into the esophagus and a bronchus.

Case 7. This 54 year old male shows a broncho-esophageal fistula on x-ray (figure 7), which later was demonstrated by esophagoscopy and bronchoscopy. Surgical intervention resulted in complete closure of the fistula.

Case 8. The x-ray (figure 8) of this 31 year old male shows a narrowing of the esophagus following numerous intrathoracic procedures in the left hemithorax, culminating in a left pneumonectomy two years previously. Dilatation with mercury-filled bougies of increasing sizes has relieved his dysphagia and regurgitation.

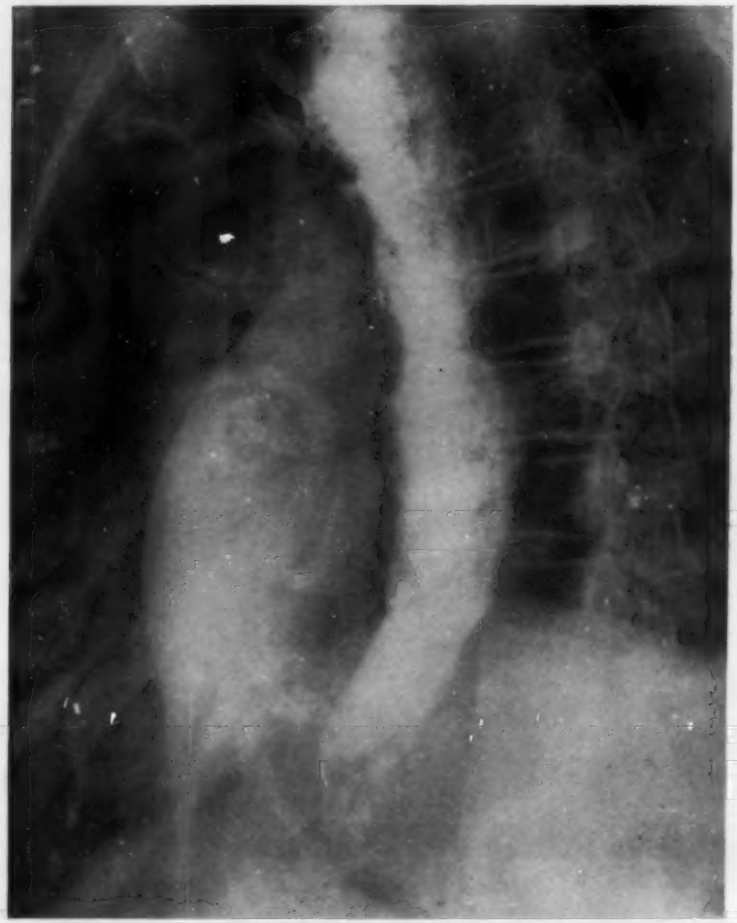

FIG. 5. *Case 5.* Idiopathic cardiospasm of eight years' duration in a man of 42. Beginning tortuosity and large amounts of retained mucus are evident.

Neoplasm ordinarily is the most serious cause of esophageal obstruction and constitutes a problem of either surgical treatment or palliation. Various measures for the latter will be discussed under treatment.

The nonsurgical treatment of esophageal obstruction is, of course, dependent upon the etiologic factors involved, and varies much from case to

case. Simple measures, such as a diet which is nonirritating mechanically, chemically and thermally, are important. In certain cases the proper chewing of food may make all the difference between complete comfort and distressing blockage. Meat, notoriously, is likely to precipitate complete ob-

FIG. 6. *Case 6.* Idiopathic cardiospasm in an 86 year old male. Large amounts of retained mucus and a filling defect due to retained food immediately above the diaphragm may be seen.

struction in the presence of a partially narrowed lumen. Obstruction from this source may at times be relieved by the ingestion of small amounts of a papain solution. The antispasmodics are not usually effective but, when they are beneficial, atropine is often the drug of choice. In nonsensitive individuals where spasm is a factor, the local action of small doses of 1 per cent pontocaine or zylcaine 15 minutes prior to eating is often very helpful.

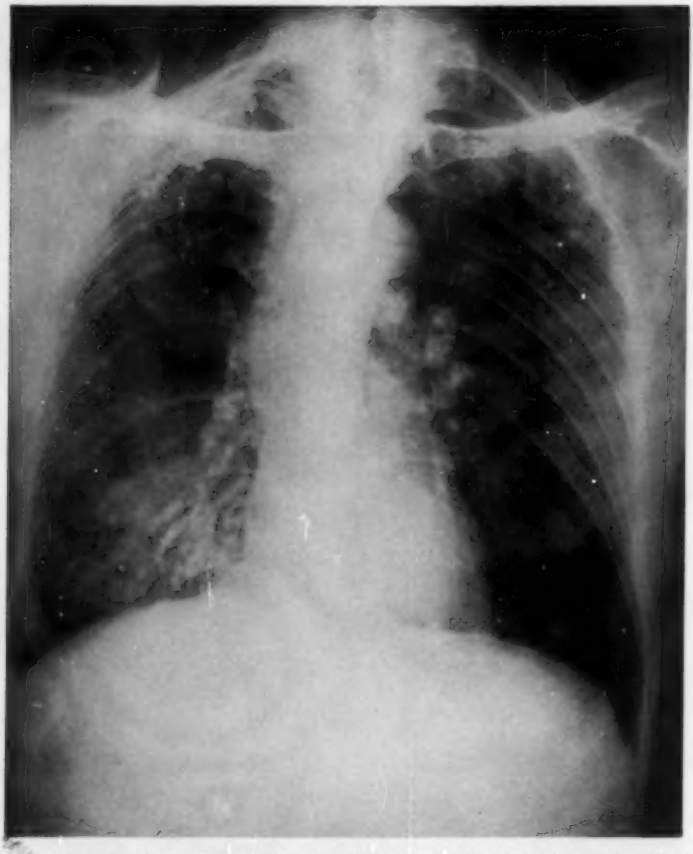

FIG. 7. *Case 7.* Opaque material in the right lower lobe of the lung following introduction into the esophagus. Broncho-esophageal fistula is present as a complication of tuberculous adenitis. Associated obstructive symptoms and the fistula were treated by extirpation of the fistula and subsequent dilatation.

In tense individuals, phenobarbital is often useful. When large amounts of mucus are present, a dram of hydrogen peroxide in a half-glass of water may have a useful cleansing action. When esophagitis is present, bismuth subcarbonate or Amphojel is indicated, and when regurgitation of gastric juice is suspected, sleeping in a head-up bed and the use of standard methods to control gastric secretion are useful adjuncts.

Mechanical dilatation, however, remains the most effective single type of treatment in the majority of cases. Figure 9 shows some of the types of instruments which may be used for dilatation, and emphasizes the difference

in procedure between the treatment of cardiospasm, in which no organic stricture is present, and the treatment of organic stricture due to fibrosis or neoplasm. The type of treatment used for the latter is of very little benefit in cardiospasm, and the vigorous methods which are useful for cardiospasm would be disastrous in the presence of organic stricture.

The filiform bougie is introduced into the channel of a stricture under direct vision through an esophagoscope for initial dilatation when the lumen is small. A metal olive on a whalebone stem (the Jackson-Plummer dilators) is introduced over a previously swallowed string. The filiforms

FIG. 8. *Case 8.* Stenosis of the esophagus following multiple intrathoracic surgical procedures for pulmonary tuberculosis.

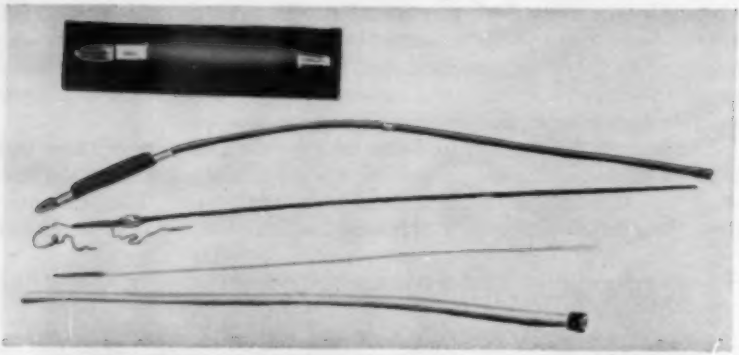

FIG. 9. From top to bottom: (1) Plummer hydrostatic dilator; (2) Jackson-Plummer dilator; (3) Jackson filiform bougie; (4) Hurst mercury-filled bougie. Inset shows balloon of Plummer hydrostatic dilator distended.

and olives are used in graduated sizes, and after the stricture has been dilated to approximately 30 French, further dilatations are more easily and conveniently given with the soft, mercury-filled Hurst bougies.

In contrast to the foregoing, the Plummer hydrostatic dilator is used effectively in the treatment of cardiospasm. After being positioned, the balloon of this instrument is distended with water pressure to 15 to 25 pounds per square inch, depending upon the individual tolerance. A single treatment of this type may produce prolonged or even permanent relief.

SUMMARY

The various types of esophageal disease producing obstruction have been reviewed and methods for the medical management of the common types have been discussed.

ACKNOWLEDGMENT

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THE SERUM POLYSACCHARIDE–PROTEIN RATIO (PR) AS A MEASURE OF RHEUMATOID ARTHRITIS ACTIVITY *

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An elevated serum polysaccharide-protein ratio (PR) occurs in active rheumatoid arthritis and certain other collagen diseases.[1] The present study is concerned with the value of this serum component in assessing the degree of rheumatoid activity.

Methods

Patients were studied at the Arthritis Clinic of University Hospitals and at the Arthritis Section of the Bone and Joint Hospital in Oklahoma City. Clinical classification of the rheumatoid state was made according to the criteria of Steinbrocker.[2] However, as this classification does not provide a scale for measuring the degree of rheumatoid activity, the patients in this report were further classified as to degree of clinical activity.

Serum nonglucosamine polysaccharide concentrations were determined by the method of Shetlar et al.[3] Total serum protein and serum albumin levels were determined by the method of Milne.[4] The polysaccharide-protein ratio (PR) was obtained by dividing the polysaccharide concentration by the serum protein and multiplying the result by 100. Erythrocyte sedimentation rates and hematocrit determinations were made by the Wintrobe-Landsberg method[5] in the clinical laboratories of University Hospitals; the sedimentation rate was corrected for the hematocrit.

Results

The PR values of 103 patients with rheumatoid arthritis are presented graphically in figure 1 after separation into four groups according to the activity of the disease. A definite correlation appears to exist between the degree of rheumatoid activity and the PR. The normal polysaccharide ratio, as determined by the method described, averaged 1.76; the inactive rheumatoid arthritis group, 1.81; the group with mild activity, 2.12; those with moderate activity, 2.43; and those with severe activity, 2.96.

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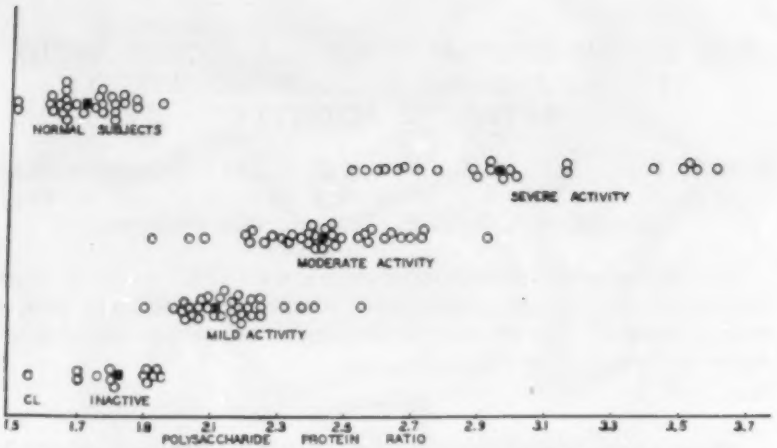

FIG. 1. Polysaccharide-protein ratio of normal subjects and patients with various degrees of rheumatoid arthritis activity. ■ represents the average for each group.

In a study of the effect of changes of rheumatoid activity on the PR value in individual patients, the patients were followed for periods of from six months to two years, during which they were subjected to various forms of therapy. Data from this study are summarized graphically in figure 2.

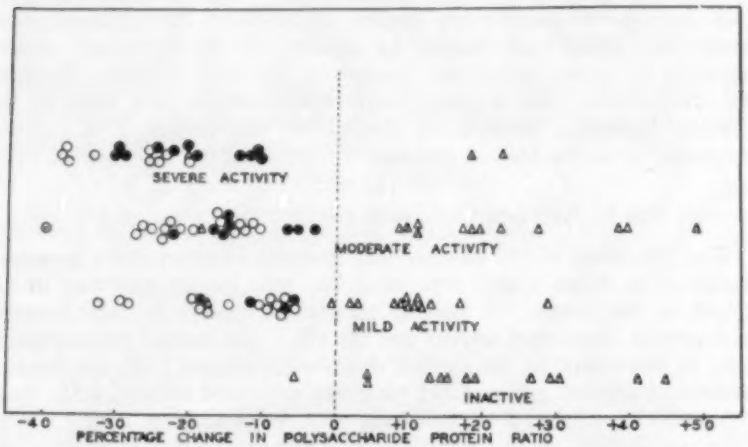

FIG. 2. Alteration of polysaccharide-protein ratio occurring with changes in rheumatoid arthritis activity. The patients were classified as to degree of clinical activity at the time of the initial polysaccharide-protein determination. Symbols representing the clinical state at the time of the subsequent PR determination, expressed as percentage changes from the first value, are indicated by: ○ substantial remission of activity (grade I), ● incomplete remission (grades II and III), and △ exacerbation (grade IV).

Only those patients manifesting a clinical change in their conditions are included in this chart; consequently, this figure shows all of the patients in the "inactive" group as undergoing exacerbation. On the basis of the variation found in normal data presented in table 1, a PR change of 10% or less was not considered to be significant. Increased clinical activity of the disease state is accompanied by a proportionate rise in PR, while remission is attended by a fall in this serum component. PR changes were of questionable value in assessing minor variations in the disease state. Usually, however, changes in the PR became manifest before the gross trend of change in clinical activity had become clearly established.

Interference from other conditions known to increase the PR, such as neoplasia, severe trauma and severe infection, proved of little consequence in the series presented; however, one patient who showed an elevated PR despite improvement in her arthritis was later found to have carcinoma of

TABLE I

Variation in Polysaccharide-Protein Ratio in the Normal Individual

Subject	Years Followed	Number Samples	Average	Range	Standard Deviation
1	3½	11	1.88	1.71–2.05	0.11
2	3	7	1.76	1.57–1.95	0.13
3	2½	6	1.66	1.60–1.74	0.06
4	2½	9	1.68	1.59–1.80	0.07
5	1½	7	1.63	1.41–1.75	0.12
6	1	8	1.59	1.43–1.92	0.15
7	2½	6	1.79	1.66–1.96	0.09
8	5½	27	1.66	1.45–1.85	0.11
Weighed Average	—	—	1.70		0.107

the colon. Two patients with incidental basal cell carcinomas of the face showed PR values consistent with their clinical rheumatoid state. A patient who sustained a fracture of the patella without exacerbation of her arthritis showed no change in PR. Two patients who developed hepatitis with jaundice during Butazolidin therapy showed temporary increases in their ratios despite clinical improvement of their rheumatoid arthritis. As serum from jaundiced patients is known to give erroneously high results, this finding was not unexpected. PR changes in three cases of lupus erythematosus and one case of Weber-Christian syndrome showed good correlation of PR values with the gross clinical course.

The corrected sedimentation rate, when correlated with the PR values, gave a correlation coefficient of 0.14, which is not of statistical significance. In general, serum albumin concentration fell with increasing rheumatoid activity and rose with improvement, although this factor was not so sensitive to clinical changes as was the PR value. Albumin values were found to be negatively correlated with PR values (figure 3), that is the albumin concentration decreased as the PR value increased. The correlation coeffi-

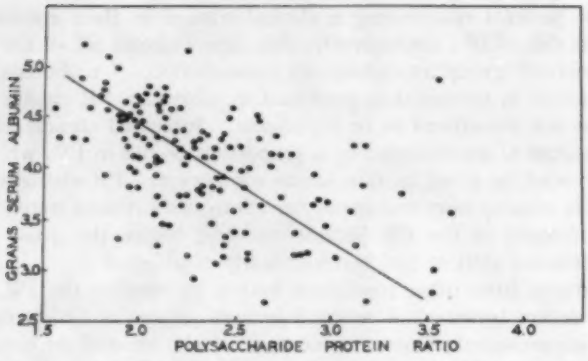

FIG. 3. Correlation of serum albumin concentration with polysaccharide-protein ratio. The regression line, calculated by the method of least squares, is also shown.

cient between PR and albumin values was —0.55, a highly significant figure statistically.

The PR remains relatively constant in the normal individual, undergoing only slight change with minor infection or minor trauma (table 1). Somewhat higher values occur in older age groups, as previously reported,[1] but this difference was not great enough to alter the interpretation significantly.

DISCUSSION

The PR appears to be an excellent objective measure of activity in the rheumatoid state. The value of this procedure as an adjunct to clinical evaluation in assessing therapeutic measures used in the treatment of rheumatoid arthritis is being further investigated and appears to hold great promise. Although other inflammatory states, neoplastic diseases and severe trauma also affect the PR, they are seldom of a severity sufficient to cause alteration in the ratio without being readily recognized. However, it is well to keep these conditions in mind when interpreting PR values.

Causes of PR changes as here described offer an interesting course for further investigation. The close association with the state of activity in certain of the collagen diseases would suggest a fundamental relationship to the basic defects of these diseases, as it appears probable that elevation of the PR can be related to the processes of inflammation.

SUMMARY

Serial determinations of the serum polysaccharide-protein ratio (PR) were made in 103 patients with rheumatoid arthritis. PR values were found to correlate with the degree of clinical activity. Improvement in the clinical state of these patients was always accompanied by a decrease in the

PR; conversely, elevated PR values occurred whenever the clinical condition became worse. Its use as an objective test in the study of rheumatoid arthritis is suggested.

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EARLY ATYPICAL MANIFESTATIONS OF LEUKEMIA *

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The diagnosis of leukemia by clinical and laboratory studies is usually not difficult. Occasionally, however, the initial manifestations of the leukemic process may be atypical and precede the onset of clinically recognizable leukemia by several years. The abnormal hematologic findings are not specific and consist of various combinations of anemia, leukopenia, neutropenia and thrombocytopenia, with a hyperactive marrow. The spleen is usually not palpable or only slightly enlarged. Initially these cases often resemble the syndrome usually designated as "primary" splenic panhematopenia.[1, 2] The following report deals with 10 patients manifesting the above findings who were studied during the past five years. Six of these patients subsequently developed typical leukemia with a rapidly fatal course. One patient died of reticulum cell sarcoma, one of aplastic anemia, and one of hemorrhage associated with thrombocytopenia. The one patient who remains alive is slowly developing hematologic changes strongly suggestive of leukemia.

Case Reports

Case 1. A 56 year old white female was admitted to the University Hospitals of Cleveland on August 11, 1950, complaining of generalized weakness. During the year previous to admission she had lost 25 pounds in weight. Physical examination revealed marked pallor. There was no general glandular enlargement, and the liver and spleen were not palpable. The remainder of the physical examination was normal. Laboratory findings revealed hemolytic anemia, leukopenia, neutropenia and thrombocytopenia (table 1). Marrow aspiration revealed marked cellularity involving both the granulocytic and erythroid elements. Megakaryocytes were present in normal rumbers. Urinalysis, total protein, A/G ratio, and blood urea nitrogen were normal. A diagnosis of "primary" splenic panhematopenia was made.

On September 1 a splenectomy was performed which did not significantly alter the hematologic findings. Pathologic examination revealed hyperemia of the spleen. The patient was discharged on September 11, 1950, having received a total of 2,000 c.c. of whole blood during the operation and postoperatively. The subsequent course was characterized by generalized weakness, purpura, weight loss, and involvement of the nerve supply of the left leg with muscular atrophy. She required multiple blood transfusions. In December 1950, a three month course of ACTH therapy was instituted. She continued to have severe anemia, moderate neutropenia and thrombocytopenia (table 1). There was a marked outpouring of normoblasts in

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From the Department of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.
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the peripheral blood (239 per 100 leukocytes), and a moderate increase in leukocyte count while on ACTH treatment.

Laboratory studies on December 7, 1951, are shown in table 1. On December 21, 1951, she was re-admitted because of severe weakness and syncope on the day of admission. Physical examination at this time revealed a 2 cm. by 2 cm. left tonsillar node and marked pallor. The laboratory findings revealed a leukocyte count of 210,000 cells per cubic millimeter, with cells typical of chronic myeloid leukemia (table 1). Marrow aspiration revealed a densely cellular marrow consisting almost completely of myeloid cells with a shift to the left. Biopsy of the left tonsillar node revealed leukemic infiltration. Despite total body irradiation therapy, urethane and blood transfusions the patient died on January 27, 1952. Autopsy showed findings characteristic of myelogenous leukemia.

TABLE I

	8/11/50	12/1/50	2/8/51	12/7/51	12/22/51
Erythrocyte count (cells/cu. mm.)	1,880,000	2,380,000	2,430,000	2,500,000	1,680,000
Hemoglobin (gm./100 c.c.)	6.0	7.2	6.7	7.0	6.0
Hematocrit (%)	21	22	24	24.5	14
MCV (cu. μ)	122	92.4	—	—	—
MCH ($\gamma\gamma$)	32.8	30	—	—	—
MCHC (%)	28.6	32.7	—	—	—
Leukocyte count* (cells/cu. mm.)	3,650	6,500	17,750	30,200	210,000
Neutrophils (%)	22	29	45	27	21
Unsegmented neutrophils (%)	10	2	7	0	5
Metamyelocytes (%)	0	1	8	2	8
Myelocytes (%)	0	1	2	3	41
Myeloblasts (%)	0	0	0	0	5
Lymphocytes (%)	64	54	32	30	2
Monocytes (%)	4	13	6	38	18
Reticulocytes (%)	3.8	8.4	9.5	0.8	4.6
Platelet count (cells/cu. mm.)	48,900	95,540	119,500	93,800	66,000
Normoblasts per 100 WBC	1	28	239	7	10
Serum bilirubin (mg. %, D/T)	.01/.46	.4/1.0	—	—	—
Fecal urobilinogen (E.U. per 100 gm.)	400	—	—	—	—
Coombs' test	—	Negative	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

Comment: This case illustrates a disease process of approximately 29 months in duration. Initially, hemolytic anemia, leukopenia, neutropenia, thrombocytopenia, and a marrow showing hyperactivity of myeloid and erythroid elements were present. The laboratory evidence of hemolysis was an elevated fecal urobilinogen and a slightly increased reticulocyte count. Splenectomy was of no benefit. Pathologically, the spleen revealed only hyperemia. ACTH therapy of three months' duration provoked a marked outpouring of normoblasts in the peripheral blood but caused no hematologic improvement. She developed myeloid leukemia with a rapidly fatal course.

Case 2. A 64 year old white male was first seen on November 10, 1950, complaining of frequent ecchymoses of nine months' duration. In February, 1950, he had noted a large spontaneous ecchymosis on the medial aspect of his left calf. Subsequently he had noted intermittent recurring ecchymoses and petechiae. During this period he had noted increasing fatigue and severe night sweats. In October,

1950, he had received two transfusions for "anemia." His past history was not pertinent. On physical examination there were scattered resolving ecchymoses on the arms and legs, and the liver was palpable 5 cm. below the right costal margin. There was no adenopathy or splenomegaly. A tourniquet test was negative. Laboratory data are shown in table 2. Bleeding time, clotting time, clot retraction and liver function studies were normal. Sternal marrow aspiration revealed a markedly hyperactive marrow involving all elements, especially the myeloid series.

No definite diagnosis was made. He continued to have purpura and ecchymoses, and during the ensuing five months developed intermittent epistaxis, hematuria and melena. When next seen, on April 19, 1951, he stated that he had lost 40 pounds and that he was becoming more fatigued. Physical examination revealed rather marked pallor, no ecchymoses, and an enlarged spleen palpable 3 cm. below the left

TABLE II

	11/10/50†	4/19/51	5/14/51	9/15/51	9/16/53
Erythrocytes (cells/cu. mm.)	4,100,000	2,730,000	4,010,000	3,560,000	2,880,000
Hemoglobin (gm./100 c.c.)	10.9	8.8	12.8	9.4	7.1
Hematocrit (%)	—	28	41	31	—
MCV (cu. μ)	—	102.5	—	—	—
MCH (γγ)	—	32.2	—	—	—
MCHC (%)	—	31.3	—	—	—
Leukocytes (cells/cu. mm.)*	6,750	8,450	6,580	6,300	156,250
Neutrophils (%)	26.0	31.5	52.5	61.0	36.0
Eosinophils (%)	6.5	5.0	2.0	1.5	0.0
Basophils (%)	4.0	0.0	3.0	1.0	0.0
Unsegmented neutrophils (%)	13.5	9.5	1.5	1.0	29.5
Metamyelocytes (%)	0.0	4.0	1.5	0.0	12.5
Myelocytes (%)	0.0	3.0	0.5	0.0	11.5
Myeloblasts (%)	0.0	0.0	0.0	0.0	10.5
Lymphocytes (%)	6.0	31.0	21.5	21.0	0.0
Atypical lymphocytes (%)	37.5	10.0	—	4.0	0.0
Monocytes (%)	6.5	6.0	17.5	10.5	0.0
Reticulocytes (%)	—	7.8	3.5	3.2	1.5
Platelet count (cells/cu. mm.)	180,960	217,000	256,640	—	36,000
Normoblasts per 100 WBC	2	0	0	1	4
Serum bilirubin (mg. %, D/T)	—	1.5/3.0	9.9/30.4	—	—
Two hr. urine urobilinogen (Ehrlich units)	—	—	7.2	—	—
Fecal urobilinogen (E.U. per 100 gm.)	—	1,600	—	—	—
Coombs' test	—	Negative	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.
† Patient had received transfusions during previous four weeks.

costal margin. The liver remained palpable 5 cm. below the right costal margin. A tourniquet test was again negative. Laboratory studies are shown in table 2. A repeat marrow aspiration showed no essential change from the previous examination. An erythrocyte osmotic fragility test showed increased erythrocyte fragility. The patient was given three transfusions of 500 c.c. whole blood and discharged.

On May 14, 1951, he was re-admitted for evaluation for splenectomy. On admission he was markedly icteric. Hepatosplenomegaly remained unchanged. Laboratory studies are shown in table 2. The cephalin flocculation test was 4 plus; the thymol turbidity was 13.0 units. Alkaline phosphatase was 33.8 units. Urine test for bile was strongly positive. Splenectomy was abandoned. A diagnosis of parenchymatous liver disease, possibly homologous serum hepatitis, was made. On bed-rest and supportive therapy the jaundice rapidly subsided, and the patient was discharged to his home on the tenth hospital day.

On August 15, 1951 he was re-admitted for reëvaluation. Laboratory studies are shown in table 2. On this admission cephalin flocculation, thymol turbidity, alkaline phosphatase and liver function studies were normal. Physical examination was unchanged.

During the next two years the patient was maintained on cortisone therapy, 0/050 mg. daily, and was asymptomatic throughout this interval. He was next seen at this institution on September 16, 1953. During this time he had gained 30 pounds. Physical examination revealed no adenopathy or hepatomegaly. The edge of the spleen was felt at the left costal margin. The laboratory findings were those of chronic myeloid leukemia (table 2). Sternal marrow aspiration revealed a markedly hyperactive marrow showing greatly increased granulocytic hyperplasia.

On December 12, 1953 he was re-admitted because of rectal bleeding and anemia. Physical examination revealed generalized petechiae and ecchymoses. The spleen was palpable 5 cm. below the left costal margin; the liver was felt 4 cm. below the right costal margin. Before laboratory studies were done he suddenly became cyanotic and died. Postmortem examination confirmed the presence of myeloid leukemia.

Comment: This case demonstrates a disease process initially manifested by hemolytic anemia, neutropenia without leukopenia and mild thrombocytopenia, a hyperactive marrow, and the absence of splenomegaly. Splenectomy was not performed. The patient was given cortisone therapy. Subsequently he developed typical chronic myeloid leukemia. Following the development of clinically recognizable leukemia the course was rapidly fatal.

Case 3. A 62 year old white male was admitted to Crile Veterans Hospital on December 4, 1951, complaining of "low blood counts." Eighteen months before admission anemia had been noted by his local physician, and he had subsequently been given intramuscular liver therapy, without clinical or hematologic improvement. Physical examination revealed moderate pallor but otherwise was not remarkable. There was no glandular enlargement or hepatosplenomegaly. Laboratory studies revealed macrocytic anemia, leukopenia, neutropenia and thrombocytopenia (table 3). X-ray studies of the heart, lungs, gastrointestinal tract, kidneys and bones were normal. Urinalysis, stool examination and routine blood chemistry studies revealed no abnormal findings. Bone marrow studies on December 19 showed a markedly hyperactive marrow involving both the myeloid and erythroid series. Megakaryocytes were increased in number.

The patient was given seven 500 c.c. transfusions of fresh blood during the ensuing five weeks. Laboratory studies on January 28, 1952, again revealed anemia, leukopenia, neutropenia and thrombocytopenia (table 3). On January 30, 1952, a splenectomy was performed, the preoperative diagnosis being splenic panhematopenia. During the operation three 500 c.c. transfusions of blood were administered. At operation the spleen was slightly larger than normal. Histologic examination of the spleen revealed acute and chronic passive hyperemia. Following splenectomy the anemia and leukopenia improved but the thrombocytopenia persisted (1/31/52, table 3).

Postoperatively the patient did poorly. He developed fever which rose to 101° to 102° F. each afternoon. The fever failed to respond to antibiotic and supportive therapy. Because of tenderness over the operative area and the development of left lower lobe atelectasis and a sterile pleural effusion at the left lung base, a diagnosis of possible subphrenic abscess was made. Laboratory studies on March 3 revealed anemia, leukocytosis and thrombocytopenia (table 3). On March 7 he was explored operatively through a left subcostal incision, but no intraperitoneal abscess was found.

TABLE III

	12/5/51	1/28/52	1/31/52	2/20/53	3/3/53
Erythrocytes (cells/cu. mm.)	1,550,000	2,560,000	4,300,000	3,400,000	2,450,000
Hemoglobin (gm./100 c.c.)	4.7	65	12.5	10.2	7.9
Hematocrit (%)	16	—	—	—	—
MCV (cu. μ)	103	—	—	—	—
MCH (γγ)	30	—	—	—	—
MCHC (%)	29	—	—	—	—
Leukocytes (cells/cu. mm.)*	2,600	1,900	6,100	9,200	49,000
Neutrophils (%)	24	14	52	56	46
Eosinophils (%)	0	0	0	0	0
Basophils (%)	1	1	2	1	0
Unsegmented neutrophils (%)	0	0	19	2	31
Metamyelocytes (%)	0	0	3	5	7
Myelocytes (%)	0	0	0	12	1
Myeloblasts (%)	0	0	0	2	2
Lymphocytes (%)	32	85	24	20	3
Atypical mononuclears (%)	0	0	0	0	10
Monocytes (%)	43	0	0	2	0
Reticulocytes (%)	0.0	0.0	0.0	0.0	0.0
Platelet count (cells/cu. mm.)	38,000	34,000	80,000	48,000	28,000
Normoblasts per 100 WBC	0	4	50	2	5
Serum bilirubin (mg. %)	0.6	—	—	—	—
Coombs' test	Negative	—	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

At the time of operation, however, the liver appeared slightly enlarged, and a biopsy was performed. Histologic examination revealed diffuse invasion of the liver by immature myeloid cells, compatible with a diagnosis of myeloid leukemia, probably acute in type. Postoperatively the patient continued to run a temperature up to 102° F., became progressively disoriented, and died on March 9 in spite of all therapy. No postmortem examination was performed.

TABLE IV

	12/1/49	9/5/50	9/24/50	8/20/52	11/22/52
Erythrocytes (cells/cu. mm.)	2,000,000	1,660,000	3,560,000	1,670,000	1,960,000
Hemoglobin (gm./100 c.c.)	6.6	5.2	10.6	5.4	5.8
Hematocrit (%)	22	20	—	—	—
MCV (cu. μ)	110	—	—	—	—
MCH (γγ)	33	—	—	—	—
MCHC (%)	30	—	—	—	—
Leukocytes (cells/cu. mm.)*	3,800	2,800	5,800	6,350	7,290
Neutrophils (%)	33.5	16.0	33.0	5.0	12.0
Unsegmented neutrophils (%)	3.0	4.0	11.0	0.0	0.0
Metamyelocytes (%)	2.0	0.0	1.0	0.0	0.0
Myelocytes (%)	0.5	0.0	0.0	0.0	0.0
Myeloblasts (%)	0.0	0.0	0.0	0.0	0.0
Eosinophils (%)	0.0	0.0	0.0	0.0	0.0
Basophils (%)	0.0	2.0	1.0	0.0	0.0
Lymphocytes (%)	44.0	72.0	45.0	38.0	30.0
Monocytes (%)	17.0	6.0	9.0	28.0	12.0
Monoblasts (%)	0.0	0.0	0.0	29.0	46.0
Reticulocytes (%)	4.2	4.1	—	—	—
Platelet count (cells/cu. mm.)	60,600	23,240	39,200	92,000	72,400
Normoblasts per 100 WBC	2	2	14	42	5
Serum bilirubin (mg. %, D/T)	.3/1.5	.15/1.0	—	—	—
Two hr. urine urobilinogen (E.U.)	5.0	4.79	3.7	—	—

* Leukocyte values are corrected for the presence of circulatory nucleated erythroid cells.

Comment: This case illustrates that the initial manifestations of the leukemic process were anemia without hemolysis, leukopenia, neutropenia, thrombocytopenia, a hyperactive marrow, and no enlargement of the spleen clinically. Histologic examination of the spleen removed only five weeks before a diagnosis of leukemia was made failed to reveal any specific morphologic lesion.

Case 4. A 63 year old white female was admitted to the University Hospitals of Cleveland on December 1, 1949, complaining of weakness of seven months' duration. Except for progressive lethargy and a weight loss of 12 pounds during this time, she had no other complaints. Physical examination was essentially negative except for pallor and hepatomegaly, the liver being palpable 3 cm. below the right costal margin. There was no adenopathy or splenomegaly. Laboratory studies revealed a macrocytic anemia, leukopenia, neutropenia and thrombocytopenia (table 4). Urinalysis, stool examination and radiographic studies of the chest, gastrointestinal tract and kidneys were within normal limits. Liver function studies were normal. Gastric analysis showed 38 units free hydrochloric acid after histamine stimulation. Sternal marrow aspiration on December 12 revealed normal cellularity, with a marked preponderance of nucleated red cells, compatible with a diagnosis of hemolytic anemia. Megakaryocytes were present in normal numbers. A diagnosis of splenic panhematopenia and hemolytic anemia was made. She was given two 500 c.c. transfusions and discharged on the nineteenth hospital day. Subsequently frequent blood transfusions were required. She was re-admitted on September 5, 1950, for splenectomy. Physical examination on admission again revealed only hepatomegaly and pallor. Laboratory studies were similar to those previously obtained (table 4). She was given 2,000 c.c. of blood, and a splenectomy was performed on the sixth hospital day. At operation the spleen was slightly enlarged. Histologic examination revealed marked hyperemia of the spleen.

Her postoperative course was uneventful. She was discharged on the nineteenth hospital day. At that time the leukocyte count had returned to normal limits, but anemia, neutropenia and thrombocytopenia persisted (table 4). Subsequently, however, there was no clinical improvement, and transfusions were required at monthly intervals. In June, 1952, ecchymoses and petechiae developed over the lower extremities, and frequent epistaxes occurred. On August 20, 1952, laboratory studies revealed immature monocytes and monoblasts in the peripheral blood (table 4). On November 22, 1952, she was admitted for the final time. Ecchymoses and purpura were apparent over the legs. Laboratory findings were diagnostic of monocytic leukemia (table 4). Her hospital course was characterized by intermittent fever and progressive bleeding. On January 10, 1953, she suddenly became comatose and died. Permission for autopsy was refused.

Comment: The initial hematologic abnormalities in this case were hemolytic anemia, leukopenia, neutropenia, thrombocytopenia and a normally active marrow with erythroid hyperactivity. The spleen was not clinically enlarged. Splenectomy caused no clinical or laboratory improvement. Histologic examination of the spleen revealed no specific morphologic lesion. Monocytic leukemia was first detected two years after splenectomy and was the cause of death.

Case 5. A 56 year old white male was admitted to Crile Veterans Hospital on June 5, 1951, complaining of easy fatigability of one year's duration. In April, 1951, anemia had been detected by his local physician, and liver injections and oral iron

therapy had been administered without response. Pertinent physical findings were pallor and hepatomegaly, the liver being felt 4 cm. below the right costal margin. There was no abnormal glandular enlargement or splenomegaly. Laboratory studies revealed anemia, mild leukopenia and neutropenia, and moderate thrombocytopenia. X-ray studies of the chest, gastrointestinal tract and osseous system were not remarkable. Urinalysis and stool examination were normal. Gastric analysis revealed 33 units of free hydrochloric acid after histamine stimulation.

Bone marrow aspiration revealed erythroid hyperplasia. A slight shift to the right of the myeloid series was present, but no immaturity of leukocytes was present. A biopsy of a small 1 cm. by 1 cm. left axillary node revealed reactive hyperplasia. During the ensuing four months parenteral vitamin B_{12}, oral iron, oral folic acid and

TABLE V

	6/6/51	10/11/51	12/19/51	3/11/52	12/22/52
Erythrocytes (cells/cu. mm.)	2,600,000	2,500,000	1,920,000	1,550,000	2,700,000
Hemoglobin (gm./100 c.c.)	8.0	11.0	5.7	5.6	6.7
Hematocrit (%)	—	—	—	—	—
MCV (cu. μ)	—	—	—	—	—
MCH (γγ)	—	—	—	—	—
MCHC (%)	—	—	—	—	—
Leukocytes (cells/cu. mm.)*	4,400	7,100	3,500	3,640	17,800
Neutrophils (%)	47	39	18	16	23
Unsegmented neutrophils (%)	0	13	5	0	7
Metamyelocytes (%)	0	0	0	0	0
Myelocytes (%)	0	0	0	0	0
Eosinophils (%)	6	3	7	1	0
Basophils (%)	0	2	2	2	0
Lymphocytes (%)	44	34	60	49	26
Monocytes (%)	3	0	8	32	21
Monoblasts (%)	0	9	0	0	23
Reticulocytes (%)	1.0	0.5	1.2	0.5	—
Platelet count (cells/cu. mm.)	150,000	480,000	406,000	220,000	—
Normoblasts per 100 WBC	2	4	22	18	41
Serum bilirubin (mg. %)	0.8	1.1	—	0.7	—
Two hr. urine urobilinogen (E.U.)	—	—	—	1.80	—
Fecal urobilinogen (E.U./100 gm.)	83	—	—	—	—
Coombs' test	Negative	—	—	Negative	—
Osmotic fragility	Normal	—	—	Normal	—

* Leukocyte counts are corrected for the presence of circulating nucleated erythroid cells.

ACTH therapy were given without hematologic benefit. Transfusions were given as needed.

On October 1, 1951, splenectomy was performed. The spleen, which weighed 520 gm., showed only passive hyperemia histologically. Liver biopsy done at the time of operation revealed no significant pathology. During the operation he received 1,000 c.c. whole blood intravenously.

Postoperatively the total leukocyte count and platelet count rose (table 5). Subsequently, however, the leukocyte and erythrocyte counts gradually decreased. The impression gained was that the frequency with which transfusions were required postoperatively was decreased.

On March 11, 1952, the patient was re-admitted complaining of recurrence of weakness and fatigability. Physical examination again revealed only pallor and a palpable liver. Laboratory studies showed anemia, leukopenia, neutropenia, and increased number of monocytes and circulating normoblasts (table 5). During the following six months the patient received 19 transfusions in order to maintain his

erythrocyte values at satisfactory levels. ACTH therapy was without benefit and did not significantly alter the peripheral blood findings.

The patient was re-admitted in December, 1952, for the final admission. Physical examination revealed numerous 4 cm. to 5 cm. erythematous indurated areas over both lower legs, pallor and hepatomegaly. Laboratory studies revealed anemia, leukocytosis, immature monocytes, monoblasts and many normoblasts (table 5). Hematologic consultation concurred with the diagnosis of monocytic leukemia. The patient ran a febrile course and died on December 28, 1952. Permission for autopsy was not granted.

Comment: The course of the patient's illness lasted two and one-half years from onset of symptoms to demise. Initially, laboratory studies showed anemia and slight neutropenia, with minimal leukopenia and thrombocytopenia. There was no evidence of hemolysis. Splenectomy had no beneficial effect, although the frequency with which transfusions were required postoperatively was slightly less. Histologic examination of the spleen revealed no specific pathologic lesion. ACTH therapy resulted in no change clinically or hematologically. Terminally, there was an increase in the leukocyte count, with outpouring of immature monocytes and normoblasts.

Case 6. A 23 month old female infant was admitted to the University Hospitals of Cleveland on July 13, 1951. Three months before admission the parents had first noted pallor and listlessness. One month before admission she developed a severe sore throat which responded to penicillin. On the day prior to admission the patient began vomiting, refused food, and was found to have a rectal temperature of 104°F. The family history and past history were not contributory.

Pertinent physical findings were as follows: rectal temperature of 38° C.; marked pallor; slightly generalized glandular enlargement; hepatomagaly, the liver edge being felt 4 cm. below the right costal margin; and splenomegaly, the spleen being palpated 5 cm. below the left costal margin. Laboratory studies revealed anemia, neutropenia and thrombocytopenia (table 6). The fecal urobilinogen was 1,200 mg. per 100 gm. The bone marrow showed increased cellularity with erythroid hyperplasia. There was no evidence of leukemia. A diagnosis of primary idiopathic hypersplenism was made, and a splenectomy was performed on August 2, 1951, after transfusions had been given.

At operation the spleen was markedly enlarged, weighing 265 gm. Histologic examination revealed myeloid metaplasia, compatible with either toxic hyperplasia, a pronounced anemia with hyperplasia of the marrow and of the spleen, or myeloid leukemia. The patient's postoperative course was excellent and she was discharged on August 9, 1951. At the time of discharge there was no anemia or leukopenia and only a moderate thrombocytopenia.

Subsequently she did fairly well. On December 17, 1951, however, she was readmitted due to reappearance of the anemia. Physical examination, aside from the operative scar, was unchanged. The laboratory findings revealed leukocytosis in addition to anemia. Myelocytes and metamyelocytes were present in the peripheral blood. Platelets were normal (table 6). Bone marrow aspiration revealed a normally active marrow, with a granulocytic-nucleated erythrocyte ratio of 2 to 1. The patient was given two 200 c.c. transfusions of whole blood and discharged.

In February, 1952, she was again admitted for transfusion therapy. On this admission clinical and laboratory data were essentially unchanged. A biopsy of an inguinal node was performed and revealed marked reticuloendothelial hyperplasia.

She was given two 200 c.c. transfusions and discharged. Laboratory studies on this admission were essentially unchanged from the previous admission.

The child was admitted on April 2, 1952, for the last time. Two days before admission she had become lethargic and anorexic. One day before admission the family physician noted cyanosis and tachypnea. Physical examination revealed an acutely ill child. The temperature was 38.1° C.; pulse, 132 beats per minute; respirations, 48 per minute. There was marked cervical adenopathy. The heart was enlarged to the left anterior axillary line; auscultation revealed a loud apical systolic murmur. Inspiratory sibilant and sonorous râles at both lung bases were heard. The liver was felt 4 cm. below the left costal margin. There was a small abscess in the right buttock. Laboratory findings were compatible with a diagnosis of myeloid leukemia. Despite antibiotics, transfusions and supportive therapy the patient developed ab-

TABLE VI

	7/14/51	8/9/51	12/17/51	4/2/52
Erythrocytes (cells/cu. mm.)	1,170,000	4,480,000	2,140,000	1,460,000
Hemoglobin (gm./100 c.c.)	3.0	12.8	6.9	5.4
Hematocrit (%)	12	—	—	—
MCV (cu. μ)	102.6	—	—	—
MCH (γγ)	25.6	—	—	—
MCHC (%)	25.0	—	—	—
Leukocytes (cells/cu. mm.)*	5,200	12,200	47,400	203,000
Neutrophils (%)	16	22	26	12
Unsegmented neutrophils (%)	12	5	12	6
Metamyelocytes (%)	4	1	8	7
Myelocytes (%)	0	1	7	23
Myeloblasts (%)	0	0	0	47
Eosinophils (%)	0	6	4	2
Basophils (%)	3	0	0	0
Lymphocytes (%)	51	51	30	3
Atypical cells (%)	12	3	2	0
Monocytes (%)	2	11	11	0
Reticulocytes (%)	0.1	0.4	1.7	—
Platelet count (cells/cu. mm.)	64,600	152,300	447,260	229,320
Normoblasts per 100 WBC	3	5	32	5
Serum bilirubin (mg. %, D/T)	—/0.42	—	0.2/1.3	—
Fecal urobilinogen (E.U./100 gm.)	1,200	—	—	—
Coombs' test	Negative	—	—	—
Osmotic fragility	Normal	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

scesses on the scalp, face, neck, extremities and trunk, and died on the 109th hospital day.

Autopsy done on the day after death revealed myeloid leukemia involving the marrow, liver, kidneys, colon and lymph nodes. The lymph nodes were massively enlarged. There were numerous abscesses of the skin. The cause of death was myeloid leukemia.

Comment: This case illustrates a disease process of approximately 15 months in duration, manifested initially by severe hemolytic anemia, thrombocytopenia, and neutropenia without leukopenia in the presence of a hyperactive marrow. It differs from the previous cases in that initially the spleen was greatly enlarged clinically and that histologic examination revealed myeloid metaplasia. Subsequent to splenectomy there was a rise in the leukocyte and thrombocyte count. The rise in the erythrocyte count was

undoubtedly due to transfusion therapy. The patient subsequently developed typical myeloid leukemia and died.

Case 7. A 58 year old housewife was admitted to the University Hospitals of Cleveland on May 21, 1949, complaining of "anemia" of seven months' duration. She denied loss of blood from any site but had noted occasional ecchymoses during the past few years. She had lost 21 pounds during the previous two years without dietary restriction. She had mild hypertension of four years' duration without referable symptoms.

Pertinent physical findings were marked obesity, pallor, and a blood pressure of 190/110 mm. of mercury. The heart was not enlarged. There was no adenopathy or hepatosplenomegaly. Laboratory studies revealed a macrocytic anemia, leukopenia and reticulocytosis. Platelets were normal (table 7). Routine blood chemistries, urine and stool examinations, and roentgenologic studies of the chest, gastrointestinal tract and colon were not contributory. A sternal marrow aspiration revealed a hy-

TABLE VII

	5/21/49	8/10/49	8/29/49	7/15/50	6/23/52	1/5/54	3/8/54
Erythrocytes (cells/cu. mm.)	2,000,000	2,100,000	3,460,000	1,700,000	1,490,000	2.50	2.52
Hemoglobin (gm./100 c.c.)	7.0	8.3	11.5	7.0	4.7	8.2	6.7
Hematocrit (%)	26	—	—	—	16	—	—
MCV (cu. μ)	130	—	—	—	—	—	—
MCH ($\gamma\gamma$)	35	—	—	—	—	—	—
MCHC (%)	26.9	—	—	—	—	—	—
Leukocytes (cells/cu. mm.)*	2,700	1,550	3,400	3,400	9,800	14,200	21,500
Neutrophils (%)	30.0	44.0	32.5	26.0	46.0	18.0	30.0
Unsegmented neutrophils (%)	26.0	13.0	20.5	17.0	15.0	1.0	3.0
Metamyelocytes (%)	0.0	0.0	0.0	0.0	2.0	7.0	3.0
Eosinophils (%)	2.5	3.0	5.5	0.0	4.0	16.0	10.0
Basophils (%)	1.0	1.0	2.5	0.0	1.0	5.0	6.0
Lymphocytes (%)	36.5	38.0	28.0	50.0	14.5	19.0	9.0
Atypical lymphocytes (%)	0.0	0.0	0.5	7.0	16.0	20.0	16.0
Monocytes (%)	4.0	1.0	10.5	0.0	1.5	14.0	23.0
Reticulocytes (%)	5.3	2.7	1.5	5.0	1.2	—	—
Platelet count (cells/cu. mm.)	304,000	348,200	—	—	—	—	560,000
Normoblasts per 100 WBC	4	1	1	2	5	2	3
Serum bilirubin (mg. %, D/T)	0.3/0.7	—	—	—	—	—	—
Two hr. urine urobilinogen (E.U.)	0.16	—	—	—	—	—	—
Coombs' test	Negative	—	—	—	—	—	—
Osmotic fragility	Normal	—	—	—	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

peractive marrow with an essentially normal cellular distribution; this finding was confirmed by sections of the aspirated marrow particles. She required transfusions every three or four weeks and was admitted on August 10, 1949 for splenectomy. Preoperative and postoperative laboratory studies are shown in table 7. Histologic examination of the spleen revealed moderate hyperplasia of the lymphoid follicles and pulp, passive hyperemia and hemosiderosis. She was discharged on August 29, 1949, having received only one transfusion during her hospital stay.

The patient improved temporarily, but gradually noted the return of symptoms referable to anemia. She required transfusions two months after splenectomy. During the following two years the patient required two transfusions every three or four months. The only significant alteration noted in her peripheral blood was a gradual increase in the total leukocyte count (table 7). In August, 1952, cortisone therapy was instituted but no beneficial effect occurred. The leukocyte count has continued to increase gradually. She continues to require two transfusions every two to three months to maintain an erythrocyte count between 2,000,000 and 2,500,000 cells per cubic millimeter. Marrow examinations continue to reveal a hyperactive marrow with normal cellular distribution. Peripheral blood studies on March 8, 1954, reveal

leukocytosis, monocytosis, eosinophilia and basophilia. Many of the monocytes are immature.

Comment: This patient demonstrates again that splenectomy in these cases has been in our experience of no lasting benefit. Anemia, probably hemolytic in nature, leukopenia without neutropenia, a hyperactive marrow and a normal sized spleen were present initially. Thrombocytopenia has never been found. Following splenectomy there was a temporary decrease in the frequency with which transfusions were required. Cortisone therapy has not been beneficial.

Whether this patient will develop leukemia remains unknown at the present time. The increase in the leukocyte count, the presence of meta-

TABLE VIII

	10/27/49	11/20/50	5/18/51	5/31/51	6/18/51
Erythrocytes (cells/cu. mm.)	3,480,000	2,520,000	2,690,000	2,820,000	2,510,000
Hemoglobin (gm./100 c.c.)	9.8	6.4	8.5	8.6	8.1
Hematocrit (%)	32.5	25	28	30	29
MCV (cu. μ)	93.3	—	—	—	—
MCH ($\gamma\gamma$)	28.1	—	—	—	—
MCHC (%)	30.3	—	—	—	—
Leukocytes (cells/cu. mm.)*	2,500	1,132	6,450	8,200	11,925
Neutrophils (%)	68	48	31.5	27	47
Unsegmented neutrophils (%)	4	4	2.0	1	1
Metamyelocytes (%)	0	0	0	0	0
Myelocytes (%)	0	0	0.5	0	0
Eosinophils (%)	1	0	0	0	0
Basophils (%)	0	1	0	0	0
Lymphocytes (%)	21	23	16.5	24	30
Monocytes (%)	4	9	2.5	3	1
Unidentified "blasts" (%)	0	0	31.0	26	11
Atypical mononuclear cells (%)	0	13	16.0	19	10
Reticulocytes (%)	9.3	—	18.1	31.0	28.2
Platelet count (cells/cu. mm.)	88,000	—	69,940	177,660	75,300
Normoblasts per 100 WBC	0	1	3.5	24	14.5
Serum bilirubin (mg. %, D/T)	.05/.3	—	—	—	—
Two hr. urine urobilinogen (E.U.)	0.55	1.3	—	—	—
Coombs' test	Negative	—	—	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

myelocytes and immature monocytes in the peripheral blood, the basophilia, and the increase in platelet count are suggestive but not diagnostic.

Case 8. A 57 year old white male was admitted to the University Hospitals of Cleveland on October 26, 1949, complaining of weakness. During the eight months previous to admission increasing fatigue, malaise and night sweats were noted. Physical examination revealed mild pallor but was otherwise normal. There was no hepatosplenomegaly or glandular enlargement. Laboratory studies revealed a moderate normochromic, normocytic anemia, leukopenia, thrombocytopenia and reticulocytosis (table 8). Sternal marrow aspiration revealed hypercellularity, with an increase in the number of granulocytes and a shift to the left. Radiographic studies of the chest, gastrointestinal tract and kidneys were normal. A transfusion of 500 c.c. of blood was administered, and the patient was discharged with a diagnosis of hemolytic anemia and panhematopenia, etiology unknown.

The patient was given another transfusion in November, 1949. Subsequently he felt well up until November, 1950, when he noted recurrence of his initial symptoms. During the first weeks of November he had three episodes of left renal colic associated with microscopic hematuria. Physical examination on November 20 again revealed no abnormalities aside from pallor. Laboratory studies are shown in table 8. During the next three months he was given four 500 c.c. transfusions. In February, 1951, he was hospitalized with bronchopneumonia. Therapy consisted of penicillin, streptomycin and blood transfusions.

On May 18, 1951, he was admitted for cortisone therapy. Laboratory studies at this time revealed 31 per cent unidentified blasts and 16 per cent atypical mononuclear cells, in addition to anemia, thrombocytopenia and reticulocytosis. Cortisone, 100 mg. intramuscularly daily, was given for 12 days, with some symptomatic improvement. Laboratory studies at the end of cortisone therapy are shown in table 8 (5/31/51). Cortisone dosage was gradually discontinued and the patient was discharged on June 4, 1951.

One week after discharge the patient noted a small nodule on the anterior surface of his right thigh; this lesion gradually enlarged. On June 18, 1951, he was readmitted for biopsy of this lesion. Physical examination revealed an 8 cm. by 8 cm. hard, subcutaneous mass in the central area of the right breast, and a 4 cm. by 4 cm. deeply erythematous tender elevated lesion on the anterior inner surface of the right thigh. Examination of the peripheral blood revealed no significant change from previous examinations (table 8).

Biopsy of the lesion on his right thigh revealed reticulum cell sarcoma. Despite therapy with nitrogen mustard, blood transfusions and antibiotics the patient died on the fifteenth hospital day. Autopsy done the day of death revealed widespread reticulum cell sarcoma of bone marrow, lymph nodes, spleen, liver and skeletal muscle. There was a widespread bronchopneumonia due to Friedländer's bacillus.

Comment: The course of this patient's illness from onset of symptoms until death was approximately 28 months. Hemolytic anemia, leukopenia, thrombocytopenia and a hyperactive marrow were found initially. Neutropenia became present during the course of the disease. The spleen was never enlarged clinically. Throughout the course of his illness repeated attempts to find evidence of a hidden lymphoma or neoplasm were made, with negative results. Abnormal immature leukocytes were repeatedly present in the peripheral blood but could not be precisely identified. Cortisone therapy resulted in a slight increase in the leukocyte count, a moderate increase in the platelet count, and a marked increase in the number of circulating normoblasts. Approximately six weeks before death the first clinical manifestation of reticulum cell sarcoma appeared.

This case illustrates the fact that the syndrome of hemolytic anemia, leukopenia, thrombocytopenia, a hyperactive marrow and a normal sized spleen may be a precursor to the *clinical* development not only of leukemia but also of lymphoma. Whether this patient had reticulum cell sarcoma throughout his whole course remains unknown. Clinically, the only abnormalities, until the final admission, were hematologic. The point to be emphasized is that when these abnormal hematologic findings are present, the presence or development of malignant reticuloendothelial disease should be strongly suspected.

Case 9. A 77 year old white female was admitted to the University Hospitals of Cleveland on February 3, 1950, complaining of progressive weakness of three months' duration. Three weeks before admission anemia had been discovered, and she was admitted for diagnostic studies. Physical examination revealed pallor. There was no glandular enlargement or hepatosplenomegaly. Examination of the peripheral blood revealed anemia, leukopenia, neutropenia, thrombocytopenia, a moderate increase in reticulocytes, and the presence of 3 normoblasts per 100 white blood cells (table 9). Gastric analysis revealed 78 units of free hydrochloric acid and 97 units total acid. Routine urinalysis, stool and blood chemistries were normal. Sternal marrow revealed an extremely hyperplastic marrow showing erythroid and granulocytic hyperplasia, with a shift to the left in both series. During the ensuing three weeks four 500 c.c. transfusions were administered. She was discharged on February 25, 1950, with the diagnosis of splenic panhematopenia.

TABLE IX

	2/3/50	3/10/50	3/25/50	3/24/51
Erythrocytes (cells/cu. mm.)	2,550,000	3,690,000	2,840,000	1,960,000
Hemoglobin (gm./100 c.c.)	6.6	10.1	8.2	6.2
Hematocrit (%)	23	—	—	—
MCV (cu. μ)	90.2	—	—	—
MCH ($\gamma\gamma$)	25.9	—	—	—
MCHC (%)	28.7	—	—	—
Leukocytes (cells/cu. mm.)*	1,200	1,300	1,800	1,180
Neutrophils (%)	38	16	24	18
Unsegmented neutrophils (%)	0	2	2	5
Metamyelocytes (%)	0	0	0	0
Eosinophils (%)	0	5	2	1
Basophils (%)	0	0	0	0
Lymphocytes (%)	56	68	71	66
Monocytes (%)	6	8	1	10
Unidentified (%)	0	1	0	0
Reticulocytes (%)	2.8	—	—	—
Platelet count (cells/cu. mm.)	66,300	—	—	—
Normoblasts per 100 WBC	3	2	8	350
Serum bilirubin (mg. %, D/T)	.22/.66	—	—	—
Two hr. urine urobilinogen (E.U.)	.76	—	—	0.17
Fecal urobilinogen (E.U./100 gm.)	130	—	—	—
Coombs' test	—	—	—	Negative

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

She was re-admitted on March 10, 1950, for splenectomy. Since her discharge she had noted the gradual recurrence of her initial symptoms. Laboratory studies were essentially unchanged (table 9). She was given 1,000 c.c. of blood preoperatively. On March 14 a splenectomy was performed. The spleen weighed 210 gm. Pathologic examination revealed slight follicular hyperplasia with focal hemosiderosis. During the operation 500 c.c. of blood were administered. She was discharged on the eleventh postoperative day. Postoperative laboratory studies revealed no improvement in her hematologic condition (table 9).

In June and December, 1950, she was admitted for transfusions because of a recurrence of her symptoms and progressive anemia. On March 24, 1951, she was re-admitted complaining of severe weakness and dyspnea. Physical examination again revealed marked pallor, but also showed a large 5 cm. ecchymotic area over the right lateral brachium and scattered petechiae over the left shoulder area and anterior chest. Examination of the peripheral blood revealed 350 normoblasts per 100 white blood cells but was otherwise unchanged (table 9). In spite of repeated

transfusions, antibiotic therapy and supportive measures the patient developed generalized petechiae and ecchymoses, ulcerative stomatitis and an ischiorectal abscess, and died on the twenty-second hospital day.

Autopsy revealed widespread hemorrhages into the skin, stomach, trachea, lungs, heart, kidney and left cerebellar hemisphere. Bone marrow from the vertebrae, ribs and femora revealed marked erythroid hyperplasia. There was moderate hemosiderosis of the lymph nodes and liver.

Comment: Splenectomy in this case of panhematopenia and marrow hyperactivity had no effect whatsoever. The fatal exitus was primarily due to hemorrhage, presumably because of the thrombocytopenia. Postmortem examination revealed no etiologic basis for the abnormal hematologic findings. Whether she might have developed leukemia or lymphoma if her course were prolonged is problematic.

Case 10. A 13 year old white schoolboy was first seen by his family doctor in May, 1951, because of a "cold." At that time pallor was noted and iron therapy prescribed. He was again seen in November, 1951, because of "acute sinusitis." Pallor was again noted and further investigations were advised. On January 27, 1952, he was admitted to Mount Sinai Hospital of Cleveland for study of his anemia. Physical examination at that time was normal except for marked pallor. Examination of the peripheral blood revealed macrocytic anemia, leukopenia, neutropenia, thrombocytopenia and a moderate increase in reticulocytes (table 10). Urinalysis, stool examinations and routine blood chemistries were normal. Marrow aspiration at that time was interpreted as showing "hyperplasia of all elements." He was given vitamin B_{12} intramuscularly for two weeks, without response.

On April 9 and April 12, 1952, respectively, the patient was seen by two hematologists, who agreed that this case represented the syndrome of peripheral panhematopenia with a hyperactive marrow. One consultant believed the spleen was palpable 2 cm. below the left costal margin. Examination of the peripheral blood again showed anemia, leukopenia, neutropenia and thrombocytopenia. The reticulocyte count was 7.8 per cent (table 10). Marrow aspiration revealed increased cellular activity, with erythroid cells, granulocytic cells and megarkaryocytes present in increased numbers. A diagnosis of splenic panhematopenia was made, and splenectomy was advised. On April 14 splenectomy was performed. The spleen was normal in size; histologic examination of the spleen revealed moderate hemosiderosis. He received two transfusions during his hospital stay and was discharged on April 19. Laboratory studies at that time showed no significant change (table 10).

There was no improvement clinically or hematologically. On August 16, 1952, he was given a transfusion of 500 c.c. whole blood and started on vitamin B_{12} and testosterone. On September 25 he was admitted to University Hospitals of Cleveland for reëvaluation. Physical examination at that time again revealed pallor and also a well healed left upper quadrant incisional scar. Laboratory studies are shown in table 10. Marrow aspiration again revealed hypercellularity of all elements. Routine urinalysis, stool examination and blood chemistries were normal. It was concluded that this case probably represented an instance of splenic panhematopenia which had failed to respond to splenectomy. He was discharged on September 27, 1952.

Subsequently he was treated with transfusions as indicated. He was admitted to the University Hospitals of Cleveland for the last time on January 24, 1953. Three days before admission he had had a shaking chill, followed by a severe sore throat. On the day before admission he became increasingly drowsy and complained of a severe headache. Physical examination revealed the temperature to be 39.8°C.

Nuchal rigidity, a positive Kernig's sign and a positive Brudzinski's sign were present. Lumbar puncture revealed the following: initial pressure, 350 mm. of water; 152 cells/cu. mm; 310 mg. of protein; culture revealed pneumococcus type 12. Blood culture revealed the same type of organism. Laboratory studies are shown in table 10. Marrow aspiration at this time revealed an extremely hypocellular marrow; the nucleated cell count was 9,000 cells per cubic millimeter, and the granulocytic-nucleated red cell ratio was 6.8. Differential studies revealed a shift to the left of the granulocytes, increase in the percentage of monocytes, and a decrease in the number of megakaryocytes. A repeat marrow aspiration on March 5 again showed hypoplasia of the bone marrow.

TABLE X

	1/27/52	4/9/52	4/19/52	9/23/52	1/24/53	3/20/53
Erythrocytes (cells/cu. mm.)	2,250,000	1,960,000	3,320,000	2,310,000	2,730,000	3,350,000
Hemoglobin (gm./100 c.c.)	7.0	7.5	10.9	9.0	8.0	10.2
Hematocrit (%)	23	24	—	27.2	—	—
MCV (cu. μ)	102.2	—	—	118	—	—
MCH ($\gamma\gamma$)	31.1	—	—	33	—	—
MCHC (%)	30.4	—	—	39	—	—
Leukocytes (cells/cu. mm.)*	3,150	3,650	5,000	2,800	4,900	2,900
Neutrophils (%)	30	37	16	15	69	9
Unsegmented neutrophils (%)	2	0	6	10	5	6
Eosinophils (%)	1	1	1	4	0	0
Basophils (%)	0	0	0	0	0	0
Myelocytes (%)	0	1	0	1	0	0
Lymphocytes (%)	63	49	68	51	16	60
Atypical lymphocytes (%)	0	0	0	1	2	12
Monocytes (%)	4	12	9	19	8	5
Plasma cells (%)	0	0	0	0	0	8
Reticulocytes (%)	3.0	7.8	4.0	2.0	—	0.3
Platelet count (cells/cu. mm.)	136,000	58,000	43,000	48,000	49,000	42,000
Normoblasts per 100 WBC	0	0	0	1	0	1
Serum bilirubin (mg. %, D/T)	—	0.4/1.5	—	—	—	—
Two hr. urine urobilinogen (E.U.)	—	—	—	0.6	—	—
Fecal urobilinogen (E.U./100 gm.)	—	—	—	300	—	—
Coombs' test	—	Negative	—	Negative	—	—
Osmotic fragility	—	Normal	—	Normal	—	—

* Leukocyte values are corrected for the presence of circulating nucleated erythroid cells.

Despite penicillin, sulfadiazine, transfusions and supportive therapy his course was progressively downward. On March 15 blood cultures revealed coagulase-positive *Staphylococcus aureus*. Erythromycin therapy was instituted. Laboratory studies on March 20 are shown in table 10. The patient died on March 23, 1953.

Autopsy performed the day of death revealed complete aplasia of the marrow of the femora, vertebrae, sternum and ribs. Postmortem blood culture revealed *Staph. aureus*. Areas of necrosis were found in the lungs, liver, kidneys and gastrointestinal tract.

Comment: Hemolytic anemia, leukopenia, neutropenia, thrombocytopenia and marrow hyperplasia were in this instance not alleviated by splenectomy. The spleen was normal in size. The course from onset of symptoms until death was 20 months. Autopsy confirmed the diagnosis of aplastic

anemia. The cause of the marrow aplasia remains unknown. Possibilities are septicemia, sulfadiazine therapy or a spontaneous transition from the previous hematologic syndrome.

Discussion

These cases demonstrate that various combinations of anemia, leukopenia, neutropenia and thrombocytopenia with a hyperactive marrow may precede the onset of clinically recognizable leukemia or lymphoma by three months to two years or longer (table 11). The average time from the date at which abnormal hematologic findings were first elicited to the onset of clinically recognizable leukemia (cases 1 through 6) was 20.6 months. Similar hematologic manifestations preceding leukemia have recently been described by Block.[3] The longest preleukemic phase described by these authors was 20 months.

In none of these patients who ultimately developed leukemia was it possible to establish the diagnosis of leukemia initially. Complete hema-

Table XI

Duration of Atypical Manifestations Prior to Development of Leukemia or Lymphoma

Case Number	Months
1	29
2	34
3	3
4	32
5	18
6	9
8	20

tologic and bone marrow studies did not reveal leukemia when these patients were first seen. Furthermore, histologic examination of the spleen revealed no specific morphologic lesion in those patients subjected to splenectomy. Thus the absence of immature cells in the peripheral blood and marrow as well as the absence of a leukemic infiltration in the spleen does not rule out the possibility that leukemia will subsequently develop in patients with pancytopenia and a hyperactive marrow.

These ten cases represent our total experience during the past five years with patients initially showing the abovementioned hematologic abnormalities. When initially seen all had anemia; in seven hemolysis was present. Leukopenia was initially seen in eight cases; neutropenia was likewise present in eight cases. All had thrombocytopenia with the exception of case 7 (table 12). Marrow aspirations uniformly revealed normal or increased cellular activity of the erythroid, granulocytic and megakaryocytic elements. In only one case was the spleen palpable. Splenectomy was done in eight of these cases without more than transient benefit.

Cases 1, 2 and 3 developed myeloid leukemia. In each instance, once clinically apparent leukemia developed the course was rapidly fatal and the

response to treatment was poor. This is in contrast to the usual course of chronic myeloid leukemia. Cases 4 and 5 developed monocytic leukemia and died. In both of these cases outpouring of immature monocytes was present, but in one instance there was no elevation of the leukocyte count and in the other only a moderate leukocytic increase.

Case 6 differs from the others in that the spleen was greatly enlarged initially and that pathologic examination of the spleen revealed myeloid metaplasia. However, it should be emphasized that hemolytic anemia, neutropenia, thrombocytopenia and a hyperactive marrow were present when the patient was first seen. Furthermore, a lymph node biopsy before splenectomy revealed reticuloendothelial hyperplasia. Although it is possible that this patient had leukemia when first seen, the initial manifestations were atypical.

TABLE XII

Summary of Cases Showing Initial Data and Final Diagnosis

Case No.	Anemia	Hemolysis	Leukopenia	Neutropenia	Thrombocytopenia	Splenomegaly	Splenectomy	Final Diagnosis
1	+	+	+	+	+	−	+	Myeloid leukemia
2	+	+	−	+	±	−	−	Myeloid leukemia
3	+	−	+	+	+	−	+	Myeloid leukemia
4	+	+	+	+	+	−	+	Monocytic leukemia
5	+	−	±	±	±	−	+	Monocytic leukemia
6	+	+	−	+	+	+	+	Myeloid leukemia
7	+	+	+	−	−	−	+	? Leukemia
8	+	+	+	−	+	−	−	Reticulum cell sarcoma
9	+	−	+	+	+	−	+	Thrombocytopenia
10	+	+	+	+	+	−	+	Aplastic anemia

Note: Marrow aspiration revealed a hyperactive marrow in all cases.

Case 7 is at present difficult to categorize. Her course, in view of past experience, suggests that leukemia is developing. There is no doubt, however, that splenectomy was valueless in this instance. Cases 8 and 10 demonstrate the development of reticulum cell sarcoma and aplastic anemia, respectively, after initially showing panhematopenia and marrow hyperplasia. Case 9 demonstrates that this syndrome in itself may be fatal before the etiology becomes apparent.

In the majority of these patients the initial findings were compatible with a diagnosis of hypersplenism or "primary" splenic panhematopenia. The presence of anemia, leukopenia, neutropenia, thrombocytopenia and a hyperactive bone marrow, and the absence of a secondary disease process in the spleen, fulfilled the criteria for such a diagnosis. In no instance, however, was splenectomy of significant benefit; this is in direct contrast to the experience of others.[4] These cases, therefore, are indistinguishable from those cases which have been described as splenic panhematopenia. It is possible that follow-up studies of cases previously described as "primary"

splenic panhematopenia may reveal the ultimate development of leukemia, lymphoma or other disease entities in a significant percentage of cases.

Summary

1. Ten cases of various combinations of anemia, leukopenia, neutropenia and thrombocytopenia are presented. Marrow aspirations were uniformly normal or hyperactive. In all instances but one the spleen was not enlarged initially.

2. Nine cases have died. Six developed leukemia. Three others died of reticulum cell sarcoma, aplastic anemia and hemorrhage associated with thrombocytopenia, respectively.

3. In none of the patients who subsequently developed leukemia or lymphoma was it possible to establish these diagnoses initially.

4. Splenectomy was valueless in the eight cases in which it was performed.

5. The relationship of these cases to "primary" splenic panhematopenia is discussed.

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CONCURRENT OBSERVATIONS OF BEHAVIOR CHANGES AND OF ADRENOCORTICAL VARIATIONS IN A CYCLOTHYMIC PATIENT DURING A PERIOD OF 12 MONTHS *†

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EMOTIONAL drives and phantasy determine the response of the psychotic individual to a greater extent than is true of the non-psychotic, who is more directly influenced by external reality. Measurable biochemical changes presumably reflect this crucial shift in the psychologic balance. Recent explorations of the pituitary-adrenal responses to stress have suggested that the activity of the adrenal cortex may provide an index of the state of certain homeostatic processes. An attempt has been made to correlate these physiologic changes with the pattern of instinctual drives and psychologic defenses as expressed in the patient's thoughts and behavior.[1] The transition from one emotional state to another in cyclothymic patients provides a special opportunity for carrying out such observations.[2]

Interpretation of the psychologic and biochemical relationships in such a study must be cautious and tentative. The available biochemical methods for studying adrenocortical activity have been developed so recently that there has not been time to establish a "normal" or "usual" background with which to compare the results found in any given individual. The accumu-

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lation of enough cross-sectional studies to achieve statistical dependability needs to be supplemented by psychologic and biochemical observations of individual patients carried out over a relatively prolonged period of time. Such longitudinal studies, of which the present report is an example, help to reduce the confusing effect of so many unknown variables because the patient to some extent becomes his own control.

I. Review of Literature

The recent advances in the relationship of adrenocortical physiology to psychiatric disturbances have been very adequately summarized by Cleghorn,[3] Hoagland,[4] Altschule,[5] Reiss [6] and Mirsky.[7] Hoagland reviews investigations of the adrenal physiology of schizophrenic patients in contrast to that of normal control subjects as carried out at the Worcester Foundation over the past decade. The evidence indicates certain qualitative and quantitative differences in the steroid metabolism of the psychotic patients compared to "normal control subjects," and also a relatively lower "stress responsivity" of the patients' adrenals to both endogenous and exogenous ACTH. In his discussion Hoagland remarks: "It is quite possible that the overproduction of some steroid substances and the underproduction of others may produce psychosis." Referring to new analytic procedures which make possible the specific qualitative and quantitative delineation of all of the steroids produced by normal people in contrast to psychotic patients, he expresses the hope of thus ultimately being able to clarify the relationship of the adrenal cortex to psychosis.

Altschule criticizes the results of the Worcester Group on the ground that other workers have not found the same abnormally small changes in blood eosinophil count or in 17-ketosteroid excretion after injection of adrenocorticotropic hormone in schizophrenia. He points out that, although all authors find a smaller than normal increase in uric acid excretion in schizophrenic patients given adrenocorticotropic hormone, this finding is common in chronic illnesses of any type. Furthermore, he reminds us that the data of these observers actually show an excessive rise of the blood sugar and of the urinary phosphate in schizophrenic patients given adrenocorticotropic hormone as compared to normals. Altschule does not accept the conclusion that the adrenal cortex in schizophrenic patients fails to respond normally during emotional stress without a demonstration of whether the test conditions actually constituted a stress to the psychotic patient.

M. Reiss investigated the day-to-day variations in the steroid hormonal excretion of mental patients. He found that the excretion rates of 17-ketosteroids and of gluco-corticoids were not necessarily parallel. He assumes from this that different adrenocortical functions are concerned with the excretion of 17-ketosteroids and gluco-corticoids, and that they are stimulated by different adrenocorticotropic hormone fractions. He adds

that in states of depression the 17-ketosteroids are usually high while the gluco-corticoids are decreased. When normal or manic features appear the steroid excretion pattern tends to be reversed.

In the present study attempts have been made to correlate changes in adrenocortical secretion with emotional changes in a cyclothymic patient over a period of 12 months. The major indices chosen to measure adrenocortical secretion have been the determinations of urinary excretion of 17-ketosteroids and glucocorticoids.

II. Psychologic Background

The Patient: The patient is the 50 year old wife of a successful investment broker and the mother of three children—a 22 year old daughter, a 21 year old son and a 15 year old daughter. Since the age of 21 she has had periods of depression lasting for several months, alternating with phases of overactivity (figure 1). During the past 10 years the intervals of relative emotional stability have lessened and the severity as well as the duration of the mood disturbances has increased.

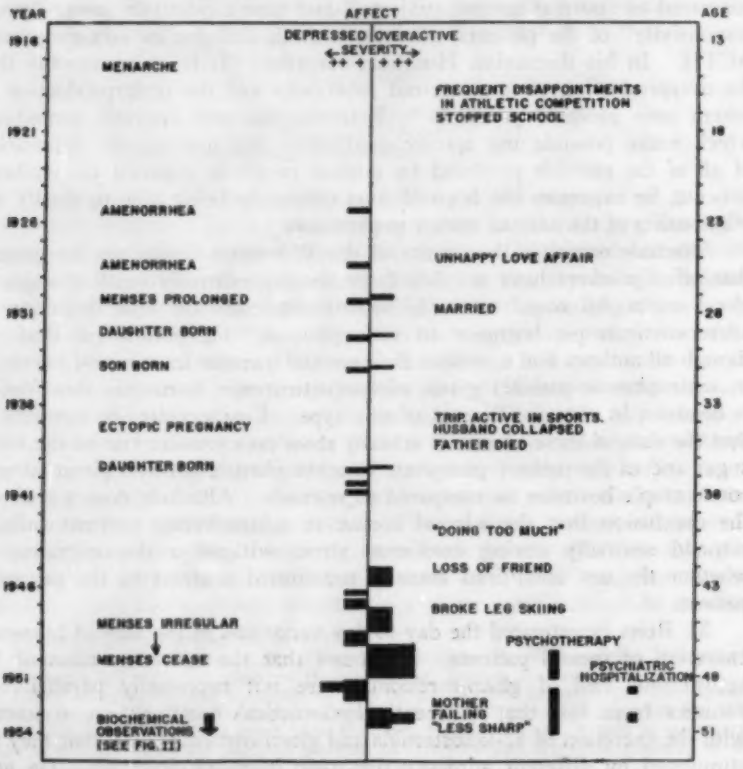

Fig. 1. Affective cycles

She has received psychotherapy for the past four and one-half years. Her initial overactivity lasted for 18 months and was then succeeded by depression for over a year, during which, at the age of 48, she was admitted to a psychiatric hospital for the first time in her life. After she left the hospital several months of unstable transition were followed by another year of overactivity, with excitement of such severity that she had to be re-admitted. Studies of her adrenocortical function began 12 months ago, at the time of her second hospitalization. Observations were made throughout this period of excitement, and have been continued since her discharge from the hospital and the resumption of her usual responsibilities.

Overactivity: Both of her overactive periods during the past four and one-half years were heralded by an urge to drink more alcohol. She began taking many trips on the spur of the moment to distant places, organized banquets and parties, and spent money freely. Although her appetite increased and she ate more food, there was not much change in her weight. She had little time for sleep and often roused members of the family or telephoned to friends at 4:00 or 5:00 in the morning, inviting them to play bridge or to join her in watching the natural beauties of the night. Libidinal drive was greatly increased. There was considerable push of speech, with a tendency to flight of ideas; for instance: "Colosseum, Nero—Nearer My God to Thee." She talked about the doings of other people but rarely about herself or her feelings. She handled her doctors by treating them as social acquaintances, offering them drinks, and keeping the conversational initiative. She rapidly made new friends but, after encouraging a precocious intimacy, dropped them and apparently never thought about them again.

Depression: During her depression she lost interest in drinking and eating. She felt guilty about the money spent on her and tried to save. She went to bed several hours earlier than usual and slept several hours later in the morning. There was definite slowing of thought and speech. Her guilty preoccupations included much concern about whether she had ruined her brain by past drinking. She felt that she should be punished and that her husband should leave her because she was such a poor wife and mother.

Projection: During her most recent depression, as well as during her excitement (in contrast to previous episodes), she expressed paranoid delusions corresponding to the dominant mood. When depressed she thought people were trying to show her she was no good and that they were maneuvering to get rid of her. During her excitement she believed one of the psychiatrists to be the President of the United States and felt she was receiving God's messages from pictures; also, that she was being watched and that people were going through her belongings (which, during her hospitalization, of course, had a certain basis in fact). Delusional phantasies about the nature of her medical treatment will be described below.

Family: Her father was an introspective, rather bitter person who had few real friends. She remembers that he was always worried about money. Apparently she thought of him as ineffectual and never felt close to him. His death when she was 34 years old did not seem to disturb her.

The patient's mother is described as vigorous, athletic and executive. She spent too much money and concealed this from her husband. Although she drinks much more alcohol than most people her age, her intellectual functions do not seem to have been much affected. The patient apparently failed all her life to experience much maternal affection in the relationship. A maternal grandfather is vividly remembered as a glamorous world traveler.

The patient's younger brother does not seem to have made much impression on her, but she has felt keenly competitive toward her older sister, whom she describes as much more beautiful than herself. She feels that her sister stole her boy friends, and she particularly resents her sister's lack of emotional warmth.

Previous Episodes: Like her sister before her, she left high school before completing her senior year. She remembers that she seemed to have some difficulty in

concentrating and was feeling very "disappointed" because she would get to the semi-finals or finals in athletic contests but was never able "to bring home the bacon" or "the cup" that "everyone at home" seemed to expect.

At the age of 22 and again at 25 she had amenorrhea for three months, accompanied by a vague feeling of not being well and of lacking energy and pep, and a difficulty in communicating with her friends or her family. The second of these episodes occurred in the setting of an unhappy love affair and this was the first occasion when she thinks of herself as having been depressed. "I felt very dull. I imagined that I must be sick but could not admit to any ache or pain. Maybe I contracted a cold. I became constipated and I wanted to be alone." During the Christmas season of the following year she became mildly elated for three or four months, followed by a depressive let-down accompanied by 10 days of menstrual bleeding.

She was married at the age of 27. Although she does not remember any unusual feelings during the course of her pregnancies, delivery of each of her three children was immediately *followed* by a definite feeling of elation. She describes herself as "feeling happier than I had reason to be," more cheerful, more interested, and talking more. "It was like a light jag." Each of these postpartum elations lasted for a few weeks and was followed by a feeling of "let-down" lasting for about three months. "I didn't have the energy. I should be happy but I wasn't."

The settings for her various mood swings since the birth of her third child have not yet been fully elucidated. On three occasions she reacted to what would seem to have been losses by becoming elated. These "losses" included being separated from a friend, breaking her leg, and realizing that her mother's health was failing and that she had become "less sharp."

Her menstrual periods became irregular when she reached the age of 45, and two years later they ceased entirely. Her most severe depression, with delusional projection and behavior requiring hospitalization for the first time, occurred after the final cessation of her periods.

Hospitalization for Depression (August 1, 1951, to November 15, 1951): In the hospital she begged, "Please punish me somehow, so I'll get better," adding, "Have them do something to me. Won't shock treatments help any?" She asked the girl who cleaned her room to let her do this herself. As she improved, she would get on her hands and knees and scrub the bathroom floors. A few weeks later she asked for more such duties, and particularly enjoyed taking care of the deteriorated patients who were incontinent of urine and feces. By November 15, 1951, she had improved to such an extent that she was discharged from the hospital and went home.

Interval Between Hospitalization for Depression and Re-admission (November, 1951, to January, 1953): After leaving the hospital she conscientiously assumed her family responsibilities and carried them out effectively except for some persistent indecision. In January, 1952, she became more preoccupied and said she felt tired. A few weeks later she expressed the belief that neighbors were trying to get rid of her, but she accepted reassurance from her psychiatrist and during the spring of 1952 her depression gradually lifted. This was characteristic of her capacity to correct her delusional phantasies even during her most disturbed periods. She was always accessible in this regard within the setting of her relationship to her psychiatrist. From May until September her visits to the psychiatrist became less frequent, and she went on more trips with her family.

By October, 1952, her lack of self-confidence and difficulty in meeting people had been succeeded by a marked increase in social and charitable activities. During the next two to three months she drank more, talked more and slept less. By the end of January, 1953, she had become much more excited and talked incessantly. She would kneel before pictures in her home and, when addressed by her husband,

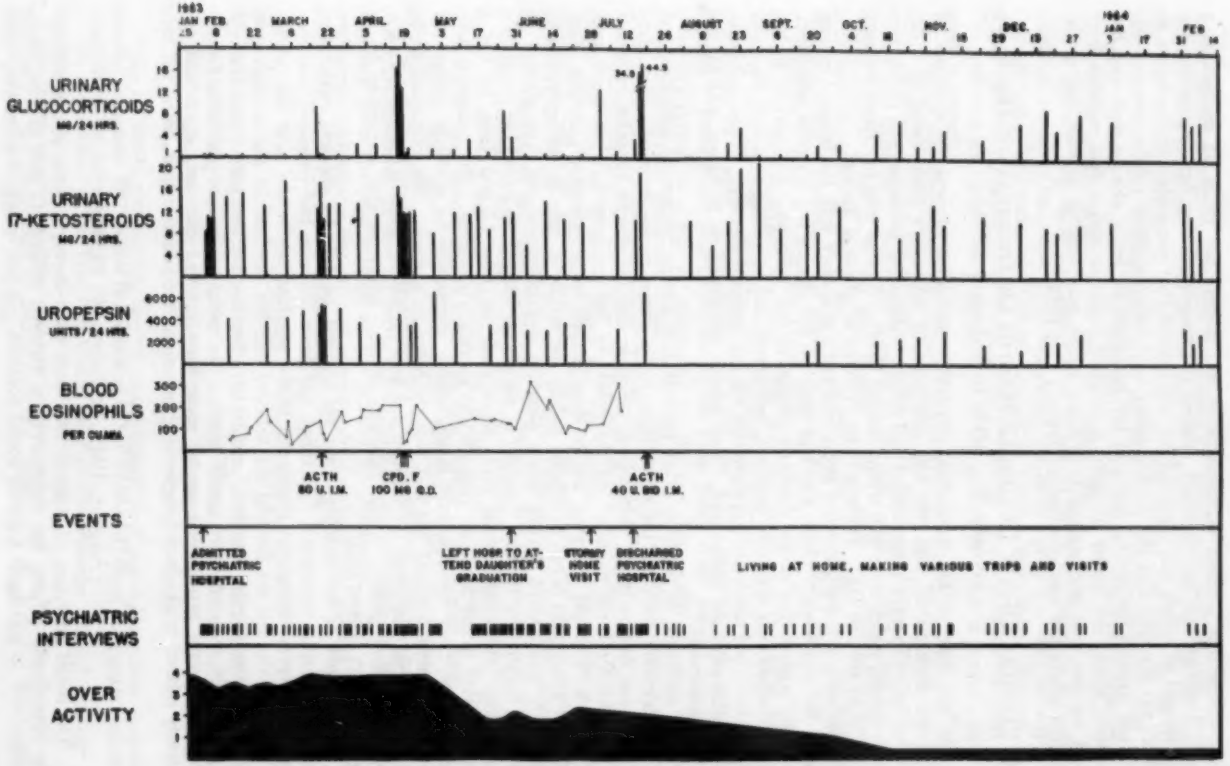

FIG. 2. Clinical course.

would freeze into a silent maintenance of this posture for 10 or 15 minutes at a time. Although she had willingly entered the hospital during her depression, she now refused to return and informed her psychiatrist that she wished to teach him as well as her husband that she did not really need either of them. After the psychiatrist had listened for several hours to her insistence on being able to deal with her problems alone, she finally accepted a sedative injection and a few minutes later asked for her coat and walked to the car which was waiting to take her to the hospital, where she was admitted on January 31, 1953.

III. Clinical Course During 12 Months Of Observation (figure 2) (January 31, 1953, to February 1954)

At the time of her admission, physical examination showed no evidence of endocrine abnormality, and this was confirmed by laboratory tests including a determination of urinary pregnanediol and follicle-stimulating hormone, and radioactive iodine uptake, which were well within normal limits. At that time her blood pressure was 120/95 mm. of Hg. There was no evidence of physical disease.

She made a fairly successful effort outwardly to comply with the hospital routine during the first week. Those who had observed her during her previous admission, however, were aware of the dramatic change in her behavior. In contrast to her earlier docility, she was now stubborn, belligerent and unwilling to accept the rules of mealtimes, bed hours and appointments for occupational therapy. When privileges were withdrawn, she complained, "You believe it's wrong to be happy, and for me to be spontaneous."

She attempted to organize other patients into groups for special activities, and on one occasion made all the decorations for a dance at the hospital. Her overactivity, and her resistant, demanding, sarcastic and belligerent behavior remained at its peak for three months. At the height of her excitement, when much preoccupied with sexual thoughts, she believed herself to be pregnant. During May, 1953, her excitement began to subside and by the middle of July her belligerence had completely disappeared. After much pleading and insistence she was allowed to leave the hospital for the first time in five months on May 27, to attend her daughter's graduation. Subsequent home visits were made on June 11 and June 15, but a weekend visit to her home on June 26 was particularly stormy. She quarreled with her husband, then spent several hours talking incessantly to a fellow patient (a chronic alcoholic woman) she had brought home as a guest. She continued to be very much disturbed about the incident and kept on talking about it for the next few days. She remembered, "I felt miserable inside. Everyone else seemed to be so happy—I can't control this."

At the time of her discharge from the hospital, on July 13, she was coöperative but still somewhat overactive. Although her outer behavior had improved, she continued to express delusional phantasies to the psychiatrist for the next few weeks. At the time she left the hospital she believed that her psychiatrist was arranging to have her sexual organs "numbed," and to have her blood drawn out so that it might be completely replaced with "good" blood. The twice-weekly venipunctures for the eosinophil counts may have provided some basis for this delusion, which was apparently related to phantasies concerning rebirth as the result of treatment.

IV. Relationship To Psychotherapist (August, 1949, to February, 1954)

The initial interview, in August, 1949, took place during a phase of overactivity. She immediately offered the psychiatrist a highball, refused to talk to him alone, and insisted on making it a purely social occasion. When he was leaving she called

to her family physician, who had introduced the psychiatrist, asking him "to bring the boy back sometime." During the next 18 months she came to see the psychiatrist but usually arrived 20 to 30 minutes late and always left early so as to keep previously arranged appointments with the dentist or the hairdresser. She made frequent trips and often called the psychiatrist unexpectedly on the long-distance telephone. For months at a time she did not come in at all.

When she was overactive she seemed to regard the psychiatrist as a necessary nuisance, complaining, "You don't ever want me to be happy. I can't do anything spontaneous. You make me feel it's wrong to have a good time. You're doing things behind my back. You're in cahoots with my husband—running him, too. I'm perfectly all right. Why do I have to see you three times a week? Once a week is enough."

During her depression she became quite clinging. She would hang on every word, pleading, "Please tell me—am I going to get better? Have I ruined my brain by my past drinking? When am I going to see you again? Can't I see you again today? I'll skip lunch if you stay longer. Please have me punished." Looking back later she believed that it was only by seeing her psychiatrist that she had been able to feel any semblance of her former self. "I recognized that I had to rely mostly on my eyes to take in what was being said. It was strange to have to understand via the eyes instead of just listening." She was also afraid that she might "absorb" insanity from the other patients. She was much preoccupied with sex and described the feeling of "being of the same fiber" (as the loved person) and "getting his essence." During her depression she wrote long notes about herself for the psychiatrist's perusal as a way of making up for the fact that he did not stay with her longer and because she found it easier to write than to talk about certain subjects. During her more excited periods she was unable to keep this log.

Toward the end of her recent hospitalization, when her overactivity was subsiding, she reported a dream about the psychiatrist: "There were many doctors, you and Jimmy (her husband). There was a big question that people were trying to answer. You are in charge and decide I'm to have electric shock treatment. You are the chairman of the group of doctors. You listen and then decide. I was happy to wake up here in my room." She had previously compared sexual sensations to being "hit on the head" and "drained" of all her blood. She was preoccupied with thoughts of being reborn and of experiencing a change in her sexual make-up.

During later interviews (January and February, 1954) these phantasies were no longer mentioned. She remained for the full hour, seemed better able to recognize emotional pressures as coming from within herself, and brought up pertinent experiences from the past as well as the present for discussion. Her high level of intelligence was always evident, and recently she has been able for the first time to accept her periods of overactivity as representing illness.

V. Psychologic Interpretation *

Rorschach, Thematic Apperception and Draw-a-Person Tests had been given to the patient in August, 1951, during her first hospital admission for depression. The psychologic tests were repeated on February 4 and February 8, 1953, a few days after her re-admission, when she had become excited and overactive.

* We are indebted to the members of the psychiatric staff at the Peter Bent Brigham Hospital, especially Dr. Arthur Valenstein and Dr. Sanford Gifford, who made valuable comments in the preparation of this manuscript.

We are indebted to Dr. Frederick Wyatt, Chief of Psychological Clinic, University of Michigan, for the report of his examination in August, 1951.

The recent psychologic tests were carried out and interpreted by Mr. Benjamin J. Murawski, of the Department of Social Relations, Harvard University, and psychologist at the Peter Bent Brigham Hospital.

Her Rorschach response this time was typical of a desperate *flight into reality*—not reality in all its complexity, however, but only in very small parts. In spite of the four hour testing time, she gave but 40 responses. These were elaborately detailed and she spent four minutes or more describing each one. The elaborations were not so much descriptions as obsessive specifications of the exact spatial relationships of one small part of the card to another. All of this clearly seemed to represent an effort to deny the existence of disturbing impressions by rigidly narrowing and controlling her field of perception. Where her restricted perception did not fulfill its defense function, she closed her eyes or hid the disturbing part of the cards with her hands. This seemed to represent use of the most primitive type of denial mechanism.

In contrast to testing carried out in August, 1951, when she was depressed, anxiety was now manifest and evidence of depressive feeling had by no means disappeared. This was interpreted either as a transition phase to a depressed state or as an incomplete warding off of depression. Along with her overactivity there were many compulsive features. Compared to her previous test functioning, there had been a dramatic shift of personality forces. During this testing there was a 50 per cent decrease in her perception of motion and a 50 per cent increase in color reactions. A decrease in the ability to perceive motion and a corresponding increase in the response to color are both apt to mean that the patient has become less aware of her internal impulses and more inclined to express them in motor behavior. It was as if her inner drives could only be handled by externalizing them and then struggling to keep control of the outer situation.

The Rorschach was re-administered after her clinical recovery (September, 1953, and January, 1954). She responded more quickly and spent less time on each response (one minute instead of four). Her phantasies seemed less accessible and she was apparently able to repress them to a greater extent. There was still considerable evidence of depression.

The patient's retrospective comments about her feelings at the time of her hospital admission express her attempted denial of depression in an unusually vivid manner: "The first week of my residence here (in the hospital) was one of easy adjustment. Not only is my philosophy to be happy no matter what the circumstances, but to exude happiness. My acting as a rule is so successful that I can nearly inwardly achieve the state. A psychiatrist can observe this and, therefore, realize that I am straining to overcome an unwelcome guest in my house."

Her maneuvers to maintain emotional control during the Rorschach test corresponded to the manner in which she attempted to control all of her personal relationships. Doctors were quickly reduced to social acquaintances. The psychiatrist became "a boy," and she kept control of the interviews by arriving late, leaving early by pre-arrangement, and writing out personal experiences instead of spontaneously talking about them. Her urge to control people and to deny the existence of unwelcome inner feelings was greatly accentuated during her period of overactivity. The extensive traveling seems to have represented an attempt to escape from her feelings by going away on long trips. This is similar to the way she propped up the last two Rorschach color cards on the desk and then viewed them from a great distance, which was interpreted by the psychologist as indicating that the full impact of the color was more than she could handle, so that she had to resort to more primitive "motor defenses," i.e., putting real distance between herself and the card.

Since she perceived her father and brother as largely ineffectual, the model for her overactivity has apparently been derived from an identification with figures from the maternal side of the family, including the executive, athletic aspects of her mother, as well as the active masculine qualities she associates with her maternal grandfather.[3] When the psychologist asked her to draw a person, she sketched a

masculinized female athlete (when depressed and again during her period of overactivity), which confirms the impression that her aggressive picture of herself has been influenced by feminine as well as masculine sources.

She has evidently responded to a feeling of loss on various occasions during her life with euphoria and elation, and the delivery of her children in a sense, of course, involved a psychologic as well as a physiologic separation.[9] During her recent psychotic episodes the manic denial of depression was incomplete, and her attempts to project her inner conflicts to the outside world were accompanied by a persistent struggle for control.

Although her phantasies included delusions of pregnancy and of her own rebirth and sexual transformation, her conflict was basically infantile (psychoanalytically interpreted as "oral"). A primitive urge to seize and absorb and her attempts to deal with her feelings of loss and self-destructive frustration dominated the clinical picture. Her resort to alcohol at the onset of each period of excitement represented her attempt to allay her anxieties by taking in a substance which quiets the conscience and encourages euphoria. Her manner of taking up and quickly dropping friendships seems to have represented an attempt to indulge a greed for emotional satisfaction as well as an avoidance of its destructive intensity.[10] Her self-punishment and self-degradation during the depression were evidently to placate the forces of her conscience which had been molded by the attitudes of a mother and father who demanded high standards but do not seem to have given her very much close affection. The Thematic Apperception Test confirmed this impression, and was interpreted by the psychologist as indicating a very early and incisive doubt of the mother's human warmth.

VI. Biochemical Study During 12 Months Of Observation

Method: A day or two after her admission she was asked whether she would be willing to coöperate with some scientific research. She was told that this would involve making 24-hour urine collections about once a week, as well as drawing specimens of venous blood before beginning each collection and also after its completion (for eosinophil counts). She responded with intelligent interest, followed the instructions with painstaking care throughout her period of overactivity, and has continued to do so since her recovery. The biochemical observations were not presented as a therapeutic measure nor as a basis for her future treatment. She knew that observations of glandular secretions were being made. In August-September, 1953, she asked to see the results and remarked after looking at them, "I am getting better."

At frequent intervals during the study, determinations of gluco-corticoids and 17-ketosteroids were carried out on 24-hour urine specimens (table 1). The urinary gluco-corticoids were measured by the method of Reddy, Jenkins and Thorn.[11] The range of values for the normal female with this method extends from 1.0 to 8.5 mg. per 24 hours, with a mean of 4.8 mg. This method determines the major metabolic products of the principal gluco-corticoid secreted by the human adrenal cortex, hydrocortisone (Compound F). Unlike previous methods (such as that used by Reiss, which measure only the free urinary gluco-corticoids), this method detects the gluco-corticoid metabolites in both the free and the conjugated form. It should

be emphasized that at least 90 per cent of the urinary gluco-corticoid metabolites exist in the conjugated form.

The urinary 17-ketosteroids were determined by a method which combines the ethylene dichloride procedure of Drekter et al.[12] with the colorimetric procedure of Holtorff and Koch.[13] The range of values with this method for the normal female extends from 7 to 15 mg. per 24 hours, with a mean of 10 mg.

TABLE 1

Urinary Gluco-corticoids and 17-Ketosteroids

Date	Hormone Administration	Gluco-corticoids (mg./ 24 hrs.)	17-Keto-steroids (mg./ 24 hrs.)	Date	Hormone Administration	Gluco-corticoids (mg./ 24 hrs.)	17-Keto-steroids (mg./ 24 hrs.)
2/3/53		<0.3	8.7	6/17		<1.0	10.6
2/4			11.4	6/24		<1.0	10.0
2/5		<0.5	10.9	7/1		12.5	
2/6		<1.0	15.4	7/7		1.4	11.8
2/11		<0.5	14.7	7/14		3.7	10.7
2/17		<0.5	15.3	7/16	ACTH 40 U bid IM	34.0	19.4
2/25		<0.5	12.8	7/17	ACTH 40 U bid IM	44.5	
3/5		<0.5	17.8	8/4			10.4
3/11		<0.5	8.4	8/12			6.0
3/17	ACTH 80 U IM	9.3	11.7	8/18			10.4
3/18		<0.5	17.4	8/23		5.5	20.0
3/19		<0.5	10.7	8/30		0.6	21.2
3/25		<0.5	13.4	9/7			9.2
4/1		2.3	13.5	9/17		<1.0	12.0
4/8		2.3	11.5	9/21		2.6	8.6
4/15			17.8	9/29		2.6	15.1
4/16	CPD F 100 mg.	16.4	15.6	10/13		4.1	11.5
4/17	CPD F 100 mg.	18.8	14.7	10/22		7.0	7.4
4/18	CPD F 100 mg.	12.8	11.9	10/29		2.2	8.9
4/19		<1.0	11.8	11/4		2.3	13.7
4/20		1.8	12.0	11/8		5.3	10.0
4/22			11.9	11/23		3.8	11.4
4/29		1.4	8.1	12/7		6.9	10.5
5/7		1.4	12.0	12/17		10.3	9.6
5/13		3.3	11.8	12/21		5.4	8.7
5/16			12.0	12/30		9.7	10.0
5/20		<0.9	8.8	1/4/54		7.2	10.5
5/26		8.7	11.0	2/1		8.5	14.2
5/29		3.7	12.0	2/4		6.8	11.9
6/3		3.7	5.9	2/8		7.1	9.2
6/10		<1.0	13.0				

The blood eosinophils were counted as described elsewhere,[14] using Hinkleman's stain.

Uropepsin was determined on 24-hour urine aliquots according to the modified method of Anson,[15] Mirsky [16] and Bucher,[17] previously reported by Spiro, Reifenstein and Gray.[18]

During the initial period of observation (psychologic overactivity) the values for urinary gluco-corticoid and 17-ketosteroid excretion were so bizarre, i.e., normal level of 17-ketosteroids associated with extremely low level of gluco-corticoids, as to necessitate special studies before interpreta-

tion was possible. For this reason, ACTH was administered on two occasions (80 units intramuscularly for one day on the first occasion, and on the second occasion 40 units intramuscularly twice daily on each of two consecutive days). This was done to determine whether the initial low excretion of gluco-corticoids represented a decrease in endogenous production of ACTH or a diminution of adrenal responsiveness to a normal output of endogenous ACTH. To determine whether the low-to-absent urinary gluco-corticoid excretion resulted from a disturbance in intermediary metabolism of the gluco-corticoids or from a diminished secretion of these substances, hydrocortisone was given in a dose of 100 mg. by mouth per day for three consecutive days. It was also hoped from this study that it would be possible to determine whether the secretion of 17-ketosteroids by the adrenal cortex could be inhibited by a high circulating level of gluco-corticoids.

Summary of Biochemical Findings: During the period of psychologic overactivity (February until July, 1953) the gluco-corticoid excretion was at an extremely low level, with the exception of the following occasions: (1) in March, when ACTH was administered, and again when it was given in July; (2) in April, when Compound F was given; (3) at the time the patient left the hospital for the first time in five months, and (4) following a stormy home visit. On these four occasions the gluco-corticoid excretion rose to normal or high levels. Following the period of psychologic overactivity there was a very definite increase of gluco-corticoid excretion to normal levels. This alteration coincided with the patient's clinical recovery.

Throughout the entire period of study it is difficult to detect any clear-cut variation in the urinary excretion of 17-ketosteroids. Even on those occasions when the patient was given ACTH there was little rise in the 17-ketosteroid excretion. Moreover, there was no fall in 17-ketosteroid levels over the three day period when Compound F was administered.

No clear-cut positive or negative correlation of eosinophil levels with the clinical state or the urinary steroid levels is apparent. It should be emphasized that factors other than changes in adrenocortical secretion may produce alteration in eosinophil levels.[19]

The 24-hour uropepsin figures * showed an average value slightly above the upper normal range, which was maintained at that level during the course of her overactive period. Although on three occasions the uropepsin increased from its baseline level to levels which were considerably higher, these changes were not of sufficient magnitude to provide the basis for any clear-cut conclusions. These three occasions were (1) the period from April 26 to May 3, which followed the administration of Compound F; (2) the period from May 24 to May 31, which coincided with the patient's departure from the hospital for the first time in five months, and (3) the period from July 12 to July 19, following the second administration of

* The uropepsin determinations and the description of the findings were made by Dr. Seymour J. Gray and Dr. Robert W. Reifenstein.

ACTH. There was an abrupt change after September 20 (at the time of her clinical recovery). Now the uropepsin levels were considerably lower than those of the earlier determinations (in the overactive period). At this time the values were within the normal range.

VII. Interpretation Of Biochemical Findings

During the period of psychologic overactivity the level of urinary 17-ketosteroids was normal while that of the gluco-corticoids was extremely low. In response to ACTH administration there was a dramatic rise in gluco-corticoid excretion, with only a very slight increase in the excretion of 17-ketosteroids.* When hydrocortisone (Compound F) was given, there was no appreciable change in the level of 17-ketosteroids, while the increase in gluco-corticoid excretion was of the same order of magnitude as that observed in normal subjects.

The abnormal pattern of 17-ketosteroid and gluco-corticoid excretion during the period of psychologic overactivity may reflect one or more of the following endogenous alterations:

1. There may have been a decrease in the output of ACTH by the anterior pituitary, leading to a diminished secretion of gluco-corticoids by the adrenal cortex, with a consequent fall in the urinary excretion of these compounds. It is to be noted, however, that while the urinary gluco-corticoids were low during the period of overactivity, the urinary 17-ketosteroid levels were normal. In the female patient with anterior pituitary insufficiency and secondary adrenal insufficiency, however, both the urinary 17-ketosteroid and gluco-corticoid levels are found to be extremely low. Hence the abnormal urinary steroid pattern observed during the period of overactivity cannot be explained solely on a pituitary basis, unless one postulates the independent secretion of two types of ACTH, one stimulating 17-ketosteroid production, the other stimulating gluco-corticoid production.

2. There may have been an alteration in the synthetic processes within the adrenal cortex. The normal urinary 17-ketosteroid level associated with a low urinary gluco-corticoid level might reflect a change in the synthetic processes within the adrenal such that the 17-ketosteroids were the predominant compounds produced with little or no synthesis of gluco-corticoids. Such a situation appears to occur in patients who have the adrenogenital syndrome due to bilateral adrenocortical hyperplasia,[20] and may possibly be present in the fetal adrenal cortex. The failure to observe

* The ACTH test reported in table 1 (March 17, 1953) and charted in figure 2 was repeated on March 13, 1954 under comparable conditions. A single injection of 80 units of ACTH was administered intramuscularly and urine was then collected for 24 hours. In March of 1953, when the patient was overactive, she excreted only 9.3 mg. of gluco-corticoids. In March of 1954, by which time she had made a clinical recovery, the gluco-corticoid value rose to 32.1 mg. for the 24-hour period following the ACTH injection—a threefold increase in response.

Gluco-corticoid as well as 17-ketosteroid values have remained at normal levels from February, 1954 to August, 1954, and during this time her general clinical improvement has been maintained.

a significant fall in 17-ketosteroid excretion during the period of hydrocortisone administration might be explained by the fact that a rather small reduction in the secretion of these compounds was masked by 17-ketosteroids derived from the administered hydrocortisone. Ordinarily in patients with increased 17-ketosteroid excretion associated with the adrenogenital syndrome due to bilateral adrenocortical hyperplasia, hydrocortisone administration leads to a fall in urinary 17-ketosteroid levels. However, in a patient with a normal level of urinary 17-ketosteroids, as was the case in this study, it is much more difficult to demonstrate conclusively an inhibition of 17-ketosteroid secretion with hydrocortisone.

3. There may have been an alteration in the intermediary metabolism of gluco-corticoids. In this patient the anterior pituitary and the adrenal cortex may have been perfectly normal, yet the gluco-corticoids may have been metabolized in such a way that a greater portion was transformed to 17-ketosteroids than occurs in the normal. It should be emphasized that the urinary 17-ketosteroids in the female consist of two main groups of com-

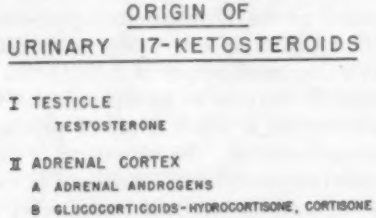

FIG. 3.

pounds (figure 3). By far the larger portion is the group of metabolites of the adrenal androgens. A small portion consists of relatively non-androgenic 17-ketosteroids arising as metabolites of the gluco-corticoids. In view of the relatively normal portion of the administered Compound F which was metabolized to urinary gluco-corticoids, it is unlikely that there was any gross disturbance in gluco-corticoid intermediary metabolism during the period of psychologic overactivity.

4. Finally, the bizarre pattern of 17-ketosteroid and gluco-corticoid levels might be due solely to an alteration in renal handling of these compounds. At the present time, in the absence of adequate methods for the determination of blood 17-ketosteroids and gluco-corticoids, it is difficult to investigate this aspect of adrenal hormone metabolism. That it is unlikely that a renal factor was responsible for the changes observed is suggested by the normal rise in gluco-corticoid levels in response to ACTH and hydrocortisone, and by the spontaneous return of the gluco-corticoid levels to normal as the patient's psychologic condition improved.

In the light of the foregoing discussion, the urinary pattern of 17-ketosteroids and gluco-corticoids during the initial period of observation

may be interpreted as follows: During this period the patient's adrenal cortex was abnormal in the sense that there was a diminished synthesis of gluco-corticoids in association with a normal synthesis of 17-ketosteroids. The output of ACTH from the anterior pituitary was diminished, but the synthetic process for 17-ketosteroids was relatively uninfluenced by the decrease in pituitary output of ACTH.

During the period of psychologic recovery, and on the five occasions previously described during the period of psychologic overactivity, the gluco-corticoid excretion rose to normal or high levels while the 17-ketosteroid levels showed little change. It would seem likely that on these occasions the adrenal cortex had responded to increased endogenous as well as exogenous ACTH with an increased output of gluco-corticoids. The failure to observe a rise in 17-ketosteroids in response to exogenous ACTH or to psychologic stress, or to detect a fall in 17-ketosteroid excretion when Compound F was administered, would seem to indicate that the production of 17-ketosteroids by the adrenal cortex was a relatively autonomous process. Studies in patients with the adrenogenital syndrome suggest that an increase in the 17-ketosteroid-gluco-corticoid ratio favors masculinization. From this it is interesting to postulate that whenever in the past there was a decreased output of ACTH this patient might have been expected to exhibit a decrease in menstruation. This, however, does not exclude the possibility of a direct effect of psychologic influences on pituitary gonadotrophin secretion. In summary, it is possible that this patient's adrenal cortex had always been abnormal in the sense that, whenever for any reason the anterior pituitary secretion of ACTH diminished, the secretion of gluco-corticoids fell while that of the 17-ketosteroids continued in a relatively independent fashion at a normal level, thus resulting in a disturbance in the urinary 17-ketosteroid-gluco-corticoid ratio.

VIII. Psychoendocrinologic Correlation

The first mild depressions when the patient was in her twenties were associated with amenorrhea, and it was during and after her menopause that her cyclothymic disturbances developed into full-fledged psychotic episodes. There seems no doubt, therefore, that the ovarian function and her emotional states are related. The elations and depressions after the birth of each child suggest further correlations in this patient between the physiology and the psychology of motherhood. In this connection it is of interest to note that in the normal female at the time of delivery there is a dramatic fall of gluco-corticoid excretion from the high levels of the third trimester to the normal to low values of the postpartum period.[21]

This study has focused on the 12 months of her most recent excitement and subsequent recovery. For several months during the period of greatest overactivity her gluco-corticoids fell below 1 mg. per 24 hours, an abnormally low value. Three times during this "low" period the gluco-

corticoid level rose to normal in response to the administration of ACTH and hydrocortisone, although these substances produced no observable effect on her mood or behavior. The gluco-corticoids also rose in association with two psychologic situations that were especially threatening to her self-control. They increased during the 24 hours before she left the hospital for the first time in five months. She had begged to be allowed out, but this meant giving up a protection against the possibility of carrying out aggressive impulses toward her family or her friends. The gluco-corticoids again rose after a stormy visit home during which she felt rejected by her husband and turned from him to her alcoholic woman friend—a situation which may well have been experienced as a repetition of her childhood disappointment in her father and a frustrated infantile appeal to her mother, who also drank large amounts of alcohol. Other visits were accompanied by a certain amount of emotional tension, but the special circumstances of these two occasions aroused her anxieties to a much greater extent. In association with a gradual clinical recovery the gluco-corticoid excretion returned to a normal level.

The infantile regressive (oral) implications of manic depressive psychoses have been repeatedly demonstrated since Karl Abraham [22] described them so vividly 25 years ago. This regression activates a ruthless drive for pleasurable intake, partially gratified during the manic phase (e.g., by phantasies of swallowing the loved object—"absorbing his essence"), and expiated to some extent by punishment during the depressive self-attack. During "normal" intervals the cyclothymic personality proves vulnerable to any interruption of ego-bolstering influences.[23] The loss of such support, more often in a setting of feeling jilted rather than merely saddened, brings the threat of raging self-destructive frustration. Manic overactivity attempts to deny the emotional loss and to externalize the self-destructive rage. Thus a state which may be interpreted as one of psychologic regression to a comparatively primitive manic denial of depression was found to be associated with a diminished excretion of gluco-corticoids and a normal excretion of 17-ketosteroids.

The increase in urinary 17-ketosteroid-gluco-corticoid ratio during a period of overactivity reflects a relative predominance of the anabolic over the catabolic phase of protein metabolism insofar as adrenocortical secretion is concerned. Could this represent the physiologic counterpart of the patient's psychologic defense against depressive drives which self-destructively threaten her own tissues?

Further observations on this patient, especially if she should again become depressed, and on others will clarify the meaning of these early observations. Whether the adrenocortical pattern of response reported here will be found in other cyclothymic patients remains to be demonstrated. Unpublished recent findings of a sharp rise in the gluco-corticoid level in a patient with acute excitement suggests that the biochemical response is quite different in states of panic before the defenses have become relatively

stabilized. In the present study an alteration in adrenocortical function has been observed in association with the activation of certain infantile emotional conflicts. If future observations confirm this, it may lead to the further elucidation of similar psychopathologic problems,[24] and also of such closely related psychosomatic disturbances as anorexia nervosa, obesity, addiction and ulcer.

Summary

1. A study of adrenocortical function was carried out in a cyclothymic patient over a period of 12 months. The blood eosinophil levels and the levels of urinary 17-ketosteroids and gluco-corticoids were the indices chosen to measure changes in adrenocortical secretion. Uropepsin determinations are also reported.

2. Gluco-corticoid excretion was abnormally low during the months of manic overactivity but rose to normal levels along with the patient's clinical recovery.

3. During the period of overactivity the gluco-corticoid values rose to normal levels in response to the administration of ACTH or hydrocortisone on three occasions, and twice in association with psychologic situations which apparently constituted a specific challenge to the patient's capacity for self-control.

4. Throughout the entire period of study the urinary 17-ketosteroid excretion remained within normal limits. This was so even on those occasions when ACTH or hydrocortisone was administered.

5. There was no apparent correlation between the blood eosinophil levels and the clinical state or the urinary steroid levels.

6. Uropepsin levels were slightly above the normal range during the period of overactivity and dropped abruptly to levels well within the normal range at the time of the patient's recovery.

7. An interpretation of the biochemical findings in relation to an alteration in pituitary-adrenocortical function is presented.

8. The patient's behavior, the nature of her phantasies, and her therapeutic relationship to the psychiatrist are described, and the results of psychologic tests are reported, including the Rorschach, Draw-a-Person and Thematic Apperception Tests. These tests were carried out during the depression which preceded her excitement, during her period of overactivity, and again since her recovery.

9. A speculation concerning the relation of adrenocortical function to a pattern of psychopathologic behavior is presented.

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MEDICINE AND THE EDUCATIONAL PROCESS *

By LAWRENCE A. KIMPTON, *Chicago, Illinois*

MR. Toastmaster, Members of the American College of Physicians:

I feel honored to be asked to address the top of a profession for which I have great respect and admiration. Lest I be misunderstood, perhaps I should add that, like a happy marriage, I love you in sickness *and* in health.

The General Chairman of your Thirty-fifth Annual Session, a most engaging fellow, made the error of saying that I could talk about anything I chose. For some reason, the complete layman with such an open invitation is drawn irresistibly to speak about a learned profession; and with an ignorance which will shortly become conspicuous I propose to address myself this evening to the topic of the medical profession and medical education. I have carefully avoided making any detailed preparation for these remarks, so that my errors will flow strictly from ignorance and not from misinformation. I am sure the problems I shall discuss are not only well known to you but probably a long way down the road toward solution. Perhaps there is a certain value, however, in the irresponsible statements of the layman who takes a short and uninformed look at the profession and the education which produces it.

It is increasingly evident to everyone that the physician within the last quarter of a century has assumed a position of new leadership within our community. He has always, of course, reflected the beliefs, the knowledge and the ethics of his time. But in more recent years the clergyman, the educator, the lawyer and the businessman have been progressively disfigured in the public eye, and the scientist and the practitioner of science have risen in public esteem. With the increase of the life span through the elimination of most serious childhood diseases, with the development of the new antibiotic wonder drugs, with the increasing public awareness of disease and the concerted attacks being made upon it, the medical profession has come into a position of renewed respect, veneration and inevitable leadership. The word of the physician carries a new weight and authority, and his judgments have an impact that extends far beyond the profession. A secret drug alleged to have an effect on cancer can upset a university, convulse a community, and unsettle the politics of a state legislature. A few pronouncements with regard to a cause of carcinoma of the lung can paralyze a large and prosperous American industry. Public confidence in medicine is so great that dollars roll and dimes march into combat against polio, heart disease, cancer and multiple sclerosis. This is an age of science, and, if we leave out the atomic physicist, the physician ranks first as scientist, philosopher and the savior of mankind.

* Address at the Annual Banquet of The American College of Physicians, Chicago, Illinois, April 8, 1954.

If this is an age in which leadership is expected of the medical profession, how well adapted is medical education to the training of leaders? From the layman's viewpoint, I am unimpressed. Nobody knows with any finality the nature of an educational program which trains leaders, but I think none of us would hesitate to say that such a program should contain a maximum of the general and humanizing studies that acquaint the student with the wisdom of the past and give him a broad knowledge of the present. It is generally thought that education for leadership not only must impart factual knowledge but must also develop real creativity; somehow through the educational process the mind must be informed and the creative imagination sharpened so that they can take wing together in disciplined flight. The doctor as leader should know the true and the good, and it would do no harm if he appreciated the beautiful. But I for one am shocked by the typical premedical curriculum. Youngsters presenting themselves for candidacy to our medical schools show a monotonous and unvarying stereotype of training involving prescribed units of physics, mathematics, chemistry, biology, and their more modern combinations. Of course there is some freedom of election allowed, but there is a list of so-called recommended subjects—chiefly from the sciences—and, such being the difficulty of entrance to our medical schools, the youngster plays it safe and does not monkey around with cultural courses that the admissions committees pay no attention to anyway. The typical premedical curriculum runs a serious risk of educating out of the student the creativity, the critical appreciation, the ability to think, which are so necessary a part of leadership. Premedics even begin to look and speak alike. As for the later medical training, it must produce competent, technically trained physicians, and there can be little room in this part of the program for a liberal education. I suggest, therefore, that we may not be educating our doctors for the position of leadership to which they are being called by the times, and that we need to take a long look, particularly at premedical training, to see if something can't be done.

Now I am well aware of the answer made to this criticism. There is an increasing amount of scientific background necessary to begin the training of the medical scientist. It is simply the case these days that he needs to know a great deal of biology, chemistry and physics, as well as biochemistry, biophysics and even higher mathematics. But where is the end of getting started to be a doctor? There is no good medical school today that does not require four years of training beyond the premedical curriculum. Add the year of internship required by the state licensing boards, and the average age of the young doctor ready to begin the practice of medicine is about 27. With the relatively recent and rapid growth of the specialty boards, three to five years of residency training are required, and the average age of the neophyte ready to enter practice creeps up to over 30. I am reliably informed that few men pass the American Board

of Internal Medicine before 32, and that almost no one under this age is able to qualify for membership in your College. I pass over the acute economic and sociologic problems created by the American College of Physicians in admitting only those who have taken the vow of poverty if not of chastity. What concerns me most is that this period of training includes the most valuable years of a man's creative life. If the physician is to assume the position of leadership which we demand of him, can he spend these years of greatest vigor and creativity in training? I trust I may express the hope that if specialization continues to grow, as it seems likely to, educational methods will be found which will enable the student to compress his essential training into fewer years and so get on with the serious business of practice, investigation and leadership.

Since I have already ventured a long way into an unknown territory, let me go a little further into this troublesome matter of specialization. In the strange and lonely job of Chancellor of a major university, I am thrown daily into casual and serious contact with men and women of widely diverse backgrounds and interests. I sense, or think I sense, the fact that the difficulties of intense specialization are being overcome in the basic disciplines of the physical and the biological sciences. The physicist, the chemist and the biologist are becoming indistinguishable, and biophysics and biochemistry, with new concepts and with radioactive tracers and high radiations as new technics, are bringing all the people in the natural sciences into increased communication and coöperation. I observe a Nobel Prize winner in physics doing remarkable work in the field of photosynthesis, and I see a physiologist working closely with a physical chemist on the problem of enzyme absorption. But when I talk to the members of the medical profession I sense, or think I sense, a decreasing mutual understanding. The diagnostic radiologist, the bone surgeon, the psychiatrist, the hematologist, seem to have less and less to say to each other. I hope this is the illusion of the layman, who doesn't understand what they are talking about in any case. Perhaps to the extent that it is true I am appealing to you internists who are central to the profession to serve as the medium of communication and to see to it that your profession does not fragment itself and endanger your science and the health of our nation. I confess to a troubled reaction to the story of the psychiatrist who, having completed his diagnosis, said to his patient, "There is nothing in the world wrong with you. It's all in your body."

There is another kind of fragmentation of your profession which is at once more disturbing and more intangible than the one I have just mentioned. I shall call it, for want of a better phrase, the disappearance of the horse-and-buggy doctor. I grew up in that part of the country where Dr. Hertzler lived and practiced, and I knew him well—a tall, gaunt frame, with the weary eyes of one who had fought through many snowdrifts to save lives and perform operations under conditions that would be deemed impossible today. He and his kind have almost disappeared. They may

not have been great doctors, judged by contemporary medical standards, but they were great men and they had something that the medical profession today runs a risk of losing. The horse-and-buggy doctor was a member of each family he attended; he had a deep and warm human sympathy and understanding; and, above all else, he had complete moral integrity. He either developed these characteristics or he did not last long in the profession. He could not hesitate where a human life was concerned. He probably would not have understood what we refer to as "social conscience," but he had it and his life was completely dedicated to the public good. The conditions under which he worked and which made him great have all but disappeared in the modern urban practice. The doctor today is a scientist, a specialized technician, and a businessman. He is surrounded by laboratory assistants, highly specialized devices for making a diagnosis, and large clinics to which referrals are made. The greatness of modern medicine lies in its science, but science is cold and hard and objective. It knows nothing of principles or social conscience or the warmth of human understanding. And the modern doctor has little opportunity in his practice to acquire these necessary virtues. But the horse-and-buggy doctor had to acquire them to survive. If the medical profession is to continue its position of leadership, it must early inculcate these virtues that were once produced by medical practice, and here I return again to education. The training of our doctors must provide for a deep sense of social responsibility, a warm understanding of men, and moral integrity. Science has transformed the profession, so that education must supply some characteristics and virtues which the practice of the profession itself once made mandatory.

I hope that you will forgive me for some rather critical remarks. I am confident that, to the extent they are valid, you have sensed the problems and have taken steps toward their solution. Our times have called your profession to a new position of responsibility and leadership. Medical education must reflect this. The obligation to determine the content and the method for such an education rests in your hands. Your profession is held in such esteem that you may requisition the resources of the nation, but you will be held to account for their use. As an educator I am at your service, and as a layman I wish you well.

CASE REPORTS

ACUTE GOUT SECONDARY TO MULTIPLE MYELOMA: A CASE REPORT *

By David Bronsky, M.D., and Arthur Bernstein, M.D., F.A.C.P.,
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Gout has been reported as occurring concurrently with the hyperuricemia found in leukemia [1] and in polycythemia vera.[2] In multiple myeloma, a condition resembling leukemia, there is also a hyperuricemia, but to our knowledge no case has been reported with concomitant acute gout. We wish to report such a case, which was further complicated by a hemorrhagic gastroenteritis following colchicine therapy.

Case Report

A 68 year old Jewish salesman entered Cook County Hospital on July 18, 1953, complaining of a painful left knee. He stated that he had been in good health until the morning of July 5, 1953, two weeks before admission, when he awoke to find his left knee swollen, red, warm and excruciatingly painful. He could not move the knee, stand on it, or bear to have anyone touch it. He applied home remedies for two weeks and then called a private physician, who advised hospitalization.

The patient had never before suffered joint pain or deformity. There was no history of arthritis or trauma. He had never had gonorrhea. There was no familial history of gout. He ate meat moderately and used alcoholic beverages sparingly. His strength was good. During the past one and one-half years he had lost five pounds in spite of good appetite. On lifting heavy weights he occasionally noticed a twinge of back pain. There was no history of peptic ulcer or gastrointestinal bleeding. He had noticed no disturbance of urinary function.

Physical examination revealed a thin, well developed white male who had a moderate degree of skin, mucosal and nail-bed pallor. Temperature was 102° F.; pulse, 94; respiration, 24; blood pressure, 148/60 mm. of Hg. The left knee was red, swollen, warm and very tender. The skin was tense and shiny, and the superficial veins were dilated. The patella was ballotable. He could not flex the knee. No other joint was involved, and there were no tophi, skeletal deformities or palpable nodules. Examination of the eyes, ears, nose, throat, lungs, abdomen and genitalia revealed no abnormalities. The heart was normal except for a soft systolic murmur at the apex. A rectal examination revealed a small prostate gland and brown formed stool which gave a negative reaction with benzidine. The neurologic examination was normal.

The urine was amber, neutral in reaction, and had a specific gravity of 1.018. There was 3 plus albuminuria. No sugar, acetone, bile, urobilinogen or formed elements were present. Examination of the blood revealed: hemoglobin, 54 per cent; red blood cells, 3,060,000; and white blood cells, 11,300. The differential white count showed: polymorphonuclears, 67 per cent; band forms, 12 per cent;

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eosinophils, 1 per cent; lymphocytes, 8 per cent; and monocytes, 11 per cent. There were slight anisocytosis, polychromatophilia and toxic changes, and one metamyelocyte was present on a smear. The sedimentation rate was 21 mm. per hour (Wintrobe). Blood nonprotein nitrogen, 43 mg. per 100 c.c.; uric acid, 11.8 mg. per 100 c.c.; total protein, 10.0 gm. per 100 c.c., with albumin, 2.5 gm., and globulin, 7.5 gm. per 100 c.c. The blood calcium was 10.2 mg. per 100 c.c., the phosphorus 5.0 mg. per 100 c.c., and the alkaline phosphatase was 3.2 Bodansky units.

X-rays revealed a generalized demineralization of the clavicles, ribs, vertebrae, pelvis and long bones. There was narrowing of the body of the second lumbar vertebra. The skull was normal. Films of the left knee revealed slight widening of the joint space and minimal arthritic changes of the patella.

Aspiration of the knee joint revealed a cloudy fluid which coagulated on standing. A small number of uric acid crystals were present on a smear. A paraffin block section revealed inflammatory cells. Routine cultures and cultures for *Mycobacterium tuberculosis* were negative.

Bence Jones protein was present in the urine.[3] Electrophoretic studies of the serum revealed a predominance of the alpha globulin fraction. An iliac crest bone marrow aspiration revealed sheets of mature plasma cells which completely replaced the bone marrow and which were regarded as characteristic of multiple myeloma.

Course in Hospital: Penicillin, aspirin, local heat applications and bed-rest were therapeutically ineffective. The patient became afebrile on the fifth hospital day, but the knee continued red, warm, swollen and tender. On the tenth hospital day he was placed on colchicine, 0.60 mg. every hour. Following the fourteenth dose he experienced considerable relief of joint pain and was able to flex the knee 90°. He also developed a diarrhea. Colchicine, 0.60 mg. three times daily, was then given, but for only one day (see below). Progressive relief of joint pain followed, and 72 hours after the beginning of colchicine therapy he was completely relieved of joint symptoms. The swelling subsided and there was complete restoration of joint motility.

The diarrhea following the initial colchicine therapy became progressively worse. Thirty-six hours after the onset of this therapy gross hematemesis and melena developed. The patient had received a total dose of 10.2 mg. of colchicine. Treatment of the gastrointestinal hemorrhage consisted of milk and cream every hour, liquid aluminum hydroxide gel every hour, atropine, 0.60 mg. every six hours, and phenobarbital, 15 mg. four times daily. Blood transfusions totaling 2,000 c.c. of whole blood were administered. The hematemesis continued three days and the gross melena five days before subsiding.

Blood chemical tests 36 hours after the onset of bleeding, were: nonprotein nitrogen, 126 mg. per 100 c.c.; creatinine, 4.2 mg. per 100 c.c.; uric acid, 17.0 mg. per 100 c.c.; phosphorus, 7.8 mg. per 100 c.c.; total protein, 10.6 gm. per 100 c.c., with albumin, 2.4 gm., and globulin, 8.2 gm. per 100 c.c. Twelve days later, and eight days after the bleeding had stopped, the nonprotein nitrogen was 47 mg. per 100 c.c., the uric acid, 13.0 mg. per 100 c.c., and the phosphorus, 4.7 mg. per 100 c.c. The urinary specific gravity after fluids had been withheld for 12 hours was 1.018. The phenolsulfonphthalein excretion was 57 per cent in two hours. The hemoglobin was 53 per cent and the red blood cells were 2,790,000. Platelets were plentiful upon a smear. The bleeding, clotting and clot retraction times were within normal limits. An attempt to detect cryoglobulin by allowing the blood to clot at body temperature and keeping the serum at 5° C. for seven days was unsuccessful.[4] A roentgenographic examination of the gastrointestinal tract failed to reveal a cause for the bleeding.

During the remainder of the patient's hospital stay there was no recurrence of bleeding or symptomatic gout. When he was last seen, three months after admis-

sion, the course of the myeloma had remained stationary, and he was free of all signs and symptoms.

Discussion

Talbott [5] states that leukemia is associated with an increased metabolism of uric acid, an increase in the size of the metabolic pool, and an increase in the concentration of uric acid in the serum. He feels that precipitation of urates in the joints, with development of acute distress, is possible because of the increased urate content of the body fluids. Hyperuricemia has long been known to exist in multiple myeloma, and it is plausible to assume that the same situation may exist here as in leukemia.

Barr [6] has reported a case of cryoglobulinemia associated with multiple myeloma. This patient had had an acute gouty episode two years prior to the diagnosis of myeloma. His uric acid level was normal at the time of the gouty episode and elevated during the course of the myeloma. He had, however, no episode of gout during the latter illness. This patient also suffered a gastrointestinal hemorrhage which may well have been connected with the large amounts of cryoglobulin present in his serum. Patients with cryoglobulinemia often present a hemorrhagic tendency. Our patient had no cryoglobulinemia.

Multiple myeloma seldom involves the joints. When it does, the offending agent is an amyloid material deposited in the joint capsule.[7, 8] This material is also deposited in striated and smooth musculature so that, clinically, macroglossia or a picture resembling rheumatoid arthritis is produced. Amyloid of the gastrointestinal tract may lead to severe hemorrhage. In our patient there were no palpable deposits of amyloid in subcutis or musculature, and his joint distress did not resemble that seen in rheumatoid arthritis.

In addition, in cases of multiple myeloma with amyloidosis the serum globulins are usually low. Thus, in our patient there was no reason to ascribe either the acute swelling of the knee joint or the gastrointestinal hemorrhage to amyloidosis. Roentgenologic examination of the gastrointestinal tract did not reveal an ulcerating lesion. On the other hand, the gastrointestinal irritant properties of colchicine are well known. A hemorrhagic gastroenteritis may follow its use.[9, 10] In our case, too, the gastrointestinal bleeding followed in the train of a severe diarrhea produced by colchicine. Attempts to explain this bleeding through other mechanisms, such as a gastrointestinal lesion, have proved unsuccessful.

Summary

We have presented a case of gout, multiple myeloma and hemorrhagic gastroenteritis. We ascribed the gouty affection of the knee joint to the hyperuricemia caused by the multiple myeloma, the hematemesis and melena to the gastrointestinal irritation following colchicine treatment.

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DYSPHAGIA OF TRANSITORY TYPE PRODUCED BY HYPERTROPHIC SPURS ON CERVICAL VERTEBRAE *

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IT is well recognized that dysphagia, as a symptom, may indicate to the diagnostician a lengthy list of lesions, benign or malignant, functional or organic, which might be the cause. In considering the functional causes, he will think of those associated with cerebrovascular disease, those due to reflexes set up by organic lesions elsewhere in the gastrointestinal tract, myasthenia gravis, globus hystericus, and "contractile ring" of the esophagus.[1]

In considering the organic causes he will think of neoplasm, particularly of the larynx and adjacent tissues, Plummer-Vinson syndrome and valvular type defects in the upper esophagus, diverticulum (usually of the pulsion type), foreign body or adjacent tissue injury, bulbar neurologic diseases, and esophagitis or adjacent abscess formation.

The cervical spine, with its mobility and its freedom from pathology of any type which produces encroachment on the hypopharynx or esophagus, might well be considered also. Immobility of the cervical spine can affect unfavorably the act of deglutition, as is demonstrated so well in rheumatoid arthritis of the cervical spine. Likewise, projection against the esophagus posteriorly by the spurs of hypertrophic arthritis can be detrimental to normal swallowing, and probably this lesion has never been considered in the past.

Dysphagia may be produced or aggravated by soft-tissue projections at the level of the interspaces in the lower cervical spine. The soft tissue prominences are usually associated with hypertrophic bone spurs at the anterior superior and anterior inferior angles of the opposed cervical vertebral bodies. In addition to the projecting spurs visible on the lateral roentgenogram, cartilage and fibrous tissue usually surround the spur, often producing a large mass. The projecting mass may be smooth or pointed, depending upon the prominence of the spur.

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The normal hypopharynx and upper esophagus, as seen on contrast study films and fluoroscopy, present a symmetric tube below the level of the epiglottis (figure 1), with anatomic narrowing of its lumen at the level of its thoracic entrance. Occasional peristaltic waves or cricopharyngeal muscle contractions are seen.[2]

Routine examination of the hypopharynx and upper esophagus for dysphagia of any type includes fluoroscopy, using oral barium and water mixture for contrast. While observing the physiology of deglutition and the anatomy of this proximal portion of the gastrointestinal tract, one of us recently noted a cascading of the barium column at a persistent point in the posterior esophageal wall in one of our patients. This led to repetition of the study and to taking of films of the area. Since that time, additional similar cases have been noted, and the films have demonstrated persistent deformity of the esophagus due to hyper-

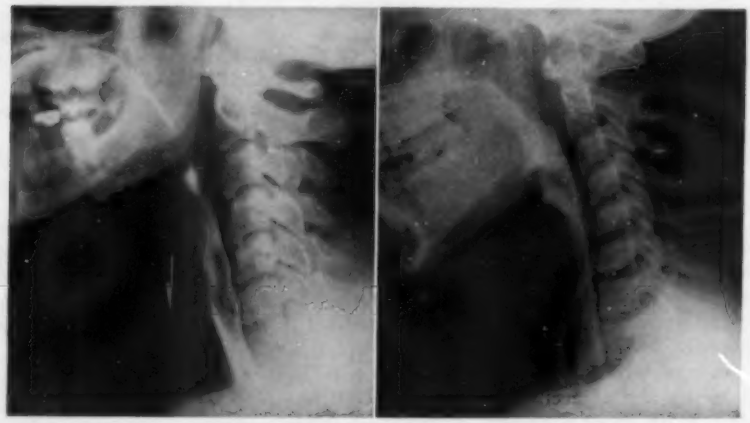

FIG. 1. Normal hypopharynx and upper esophagus as outlined by barium swallow. Note peristaltic waves of normal depth at vertebral interspaces.

trophic spurs on cervical vertebrae. As a result, we have concluded that the posterior hypopharynx and esophagus should be carefully examined under fluoroscopy in all cases of dysphagia, particularly when no other pathology is apparent.

If a suspicious posterior wall defect or cascade flow of the barium is noted, then films should be made in the lateral projection through the cervical spine. The patient is placed in the upright position, with neck slightly extended, to accentuate any protrusion. A barium-water mixture is swallowed at the time of exposure for contrast. Barium mixture of ordinary fluid viscosity and thickness is used to avoid the lumping or fragmentation often encountered in thick mixtures. Mattson [3] has devised an excellent method for visualization of this area, using simultaneous fluoroscopy and radiography during swallowing.

Studies of normal control patients show that if the cervical spine is free of hypertrophic changes, the posterior wall of the hypopharynx and esophagus is smooth in the cervical levels. If hypertrophic spurs are present, then of tissue

projections are often present (and are often asymptomatic). Peristaltic waves and mucosal buckling may simulate this defect but the findings are not so constant, nor are they exactly at the vertebral interspace level.

Two clinical cases are presented of patients of ours who first drew our attention to this lesion producing dysphagia.

Case Reports

Case 1. A 47 year old married woman was first seen on August 13, 1951, but first complained of swallowing distress on September 2, 1952. She felt as though she had an obstruction in her throat, had difficulty in swallowing, and described a sensa-

Fig. 2. *Case 1.* Hypertrophic spurs and soft tissue components project into the posterior esophagus at the sixth cervical vertebral interspace.

tion of "glue" accumulating in the throat. At her request she was referred to a throat specialist, who reported no throat pathology. Because of continuation of symptoms and of chronic cancerphobia in this patient, she was x-rayed on September 17, 1952, and the cervical vertebral lesion was noted. The lesion was explained carefully to the patient and the films (figure 2) were demonstrated to her. A mild sedative to be taken at meal times was prescribed. On March 2, 1953, she reported she had not been bothered lately. However, when last seen, on August 31, 1953, she again complained of throat obstruction (worse after having recently resumed smoking). Again she presented the general problem of cancerphobia, and requested that she be referred to a "cancer clinic." It was noted that her menstrual periods had been a little irregular in the last few years.

Case 2. A 46 year old married woman was first seen on January 8, 1947. On December 30, 1949, she first mentioned that her throat got dry and that she developed "spasm of the nerves" in her throat when she got "hurried and nervous." She constantly felt obstruction to swallowing and breathing. Menstrual periods had recently become erratic. X-rays were taken which showed the hypertrophic spurs (figure 3). Treatment consisted of careful explanation of the probable cause of her symptoms and of a demonstration of the films. Mild sedatives were given at meal times. On January 6, 1950, she reported that she felt much better in every way. She was not seen again until November 20, 1952, at which time she was in status asthmaticus. She had developed asthma for the first time in her life in June, 1952, and had not been relieved since. The asthma persisted when she was last seen, on May 22, 1953. On numerous occasions in 1952 and 1953 she was questioned regarding dysphagia. She denied any symptoms and only vaguely recalled her previous

FIG. 3. *Case 2.* Esophageal defect similar to that demonstrated in figure 2. The pattern is accentuated because the hypertrophic changes are more marked.

bitter complaint. When last heard from (by letter on November 24, 1953), she was undergoing psychotherapy in another city where she had been hospitalized for status asthmaticus.

It is apparent that this is a benign type of dysphagia and that symptoms are apparent only at times. In both of the cases reported the patients could be described as anxious and phobic. There is little in their history to suggest an organic cause for their dysphagia, and both of these patients would have been said to have simple globus hystericus were it not for the x-ray evidence of pathology.

Neither patient had a major complaint of arthritis. Thus, the cervical hypertrophic spurs were not associated with major joint disability. Both patients were pre-menopausal. Simple reassurance and sedation were followed by remission of symptoms.

A B C

FIG. 4. Additional cases not reported above. All of these cases complained of occasional upper esophageal dysphagia. *A*. Posterior esophageal defect at the sixth cervical vertebral interspace. *B* and *C*. Posterior wall defects at two interspace levels (fifth and sixth cervical).

SUMMARY

In the differential diagnosis of dysphagia one must consider deformity of the esophagus by protruding spurs of cervical hypertrophic arthritis of the spine. This lesion is easily demonstrated by barium swallow with the cervical spine slightly extended. The lesion is apparently comparatively benign, and symptoms are relieved by reassurance and sedation. The lesion is not necessarily a part of severe generalized hypertrophic arthritis.

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PERICARDIAL COELOMIC CYST SIMULATING CHRONIC PERICARDIAL EFFUSION: REPORT OF A CASE*

By FRANCIS S. GERBASI, M.D., *Long Beach, California*

ALTHOUGH pericardial cysts are relatively rare, recent medical literature has contained several excellent reports [1, 2, 3] concerning the etiology, pathology, diagnosis and treatment of these anomalies. An extensive review of the publications on this subject, however, shows that cysts of such size, configuration and location as to be confused with chronic pericarditis with effusion are exceedingly rare. Inasmuch as the cyst herein reported was difficult to differentiate from pericardial effusion and appears to be the largest coelomic cyst ever described, it is felt that it may be of interest.

CASE REPORT

A 34 year old white woman was admitted to the University Hospital on October 1, 1952. She had been referred by a physician because of a routine chest roentgenogram on September 22, 1952, which he interpreted as showing "fluid around the heart."

Two and one-half years previously the patient had begun to notice "pressure pain" in the upper portion of the left chest anteriorly; any type of exercise characteristically provoked this pain to radiate posteriorly. Running produced extreme dyspnea and led to a pain or sensation which she described as being "as if something had to break under my left chest." This discomfort prevented her from lying on her left side; sometimes it radiated into the left upper extremity.

Her physician treated her for "pleurisy," but without benefit. During the two years these symptoms persisted she also had a nonproductive cough and numerous episodes of upper respiratory infections. None of the several tuberculosis survey chest roentgenograms made since 1949 had been reported to her as abnormal. A preëmployment chest film revealed the gross thoracic abnormality for which she was referred to the University Hospital.

* Received for publication November 6, 1953.
From the Department of Surgery, University of Michigan School of Medicine, Ann Arbor, Michigan.

The physical examination revealed a well developed, slightly undernourished white woman who did not appear ill. The blood pressure was 110/80 mm. of Hg. The pulse was 64/minute and the respirations were 18/minute. The only positive physical findings were noted in the chest. There were dullness, decreased breath sounds and decreased tactile fremitus over the lower portion of both thoraces anteriorly. By percussion the left border of cardiac dullness was 1 cm. lateral to the left midclavicular line; the right border was percussed 2 cm. lateral to the right mid-

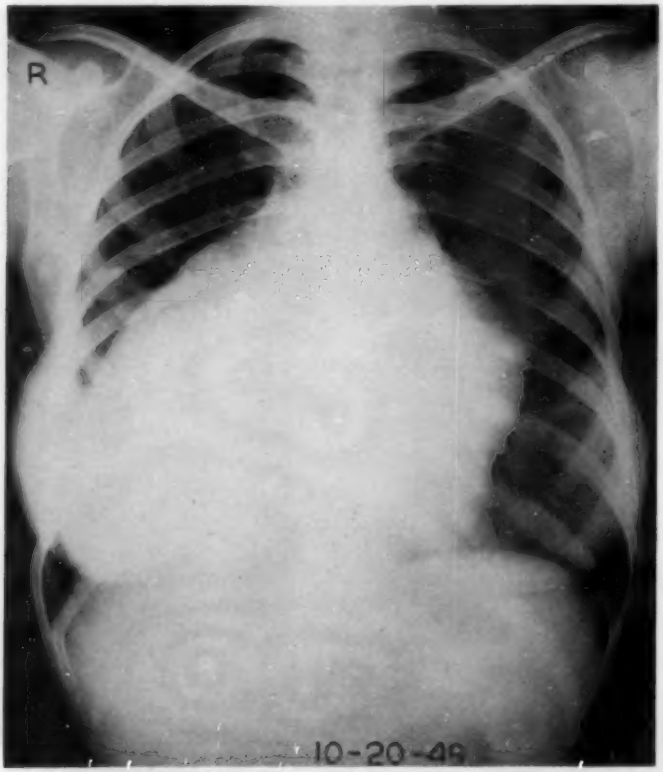

FIG. 1. Pre-admission x-ray of October, 1949, revealing a large abnormal shadow about the heart.

clavicular line. No murmurs were audible. There was no distention of the neck veins, although one observer felt that a hepatojugular reflux could be elicited. The abdomen was negative. Routine examinations of the blood and urine were normal. The venous pressure in the right forearm (patient reclining) was found to be equivalent to 130 mm. of water. The electrocardiogram showed "normal tracing except for a rather low voltage." The basal metabolic rate was plus 5.

The pre-admission chest films were secured for review (figure 1), and new films in several projections were obtained (figures 2, 3). In addition, the patient

was fluoroscoped and rapid sequence angiocardiograms were obtained. The following comment was made: "Several possibilities should be included in the differential diagnosis of this patient's thoracic abnormality. Inter-auricular septal defect may produce extensive right auricular enlargement and this is suggested by the apparent enlargement in the region of the right auricle seen in lateral view. However, review of previous routine survey films taken elsewhere between 1949 and 1952 shows that the apparent enlargement of the right side of the heart and the undivided portion of

FIG. 2. Roentgenogram of the chest made a few days after admission, in the upright position, showing the large abnormal shadows in both hemithoraces. Note the area of radiolucency just to the right of the lower thoracic spine, suggesting that the abnormal shadows are not due to a pericardial effusion. Also note that the shadows have increased in size since October, 1949.

the pulmonary artery, suggested in the films taken at the University Hospital, is not actually the case. Also, it seems inconceivable that if this patient's abnormality represents heart disease she could now have no signs of cardiac failure. Another possibility is extensive pericardial effusion. However, fluoroscopically definite pulsations were seen at the borders of the mass, and again one is led to the conclusion that the abnormality represents a huge anterior mediastinal cyst, perhaps, but im-

probably, pericardial in origin. It is believed that the abnormality is benign, a huge cystic teratoma being a likely possibility."

The angiocardiograms were interpreted as follows: "This examination shows without doubt that the large anterior mass containing fluid is not cardiac in origin and does not appear to embarrass cardiac activity. Undoubtedly, it compresses the right lung. No evidence of invasion of the intrathoracic vascular structures is found. Since a fluid-filled cyst is suspected perhaps aspiration would be diagnostic."

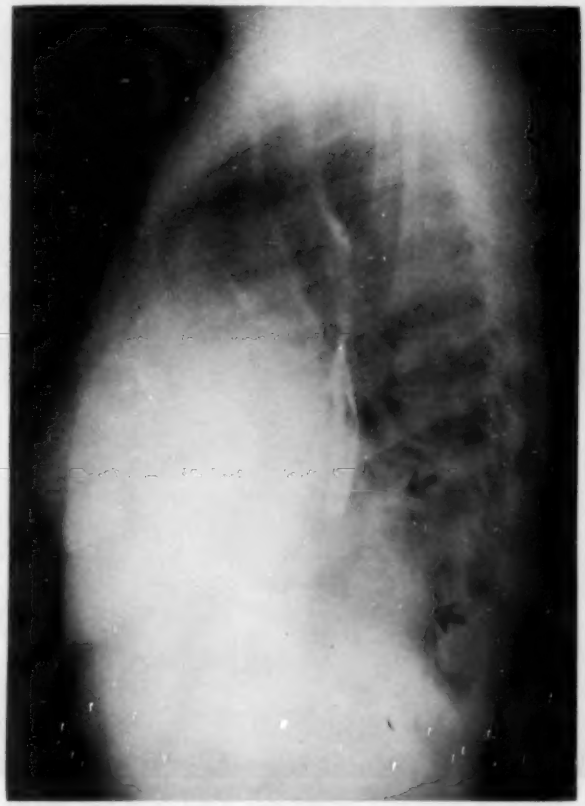

FIG. 3. Lateral view of the chest, demonstrating the lateral and posterior extension of the cyst.

The large mass was aspirated in the fourth intercostal space on the right side; 800 c.c. of clear, straw-colored fluid were withdrawn and partially replaced by the injection of air. The specific gravity of this fluid was 1.007. A stained smear of the fluid did not reveal microörganisms, and no growth was obtained upon bacteriologic culture.

Additional x-rays were made (figure 4), with the following comment: "Although

previous reports have suggested rather dogmatically that the patient's abnormality represented a huge anterior mediastinal cyst, such does not appear the case. The findings at this time must be interpreted as due to a large pericardial effusion. This is somewhat difficult to understand in view of the patient's original film made 3 years previous to admission (figure 1), which does not have the configuration of a pericardial effusion."

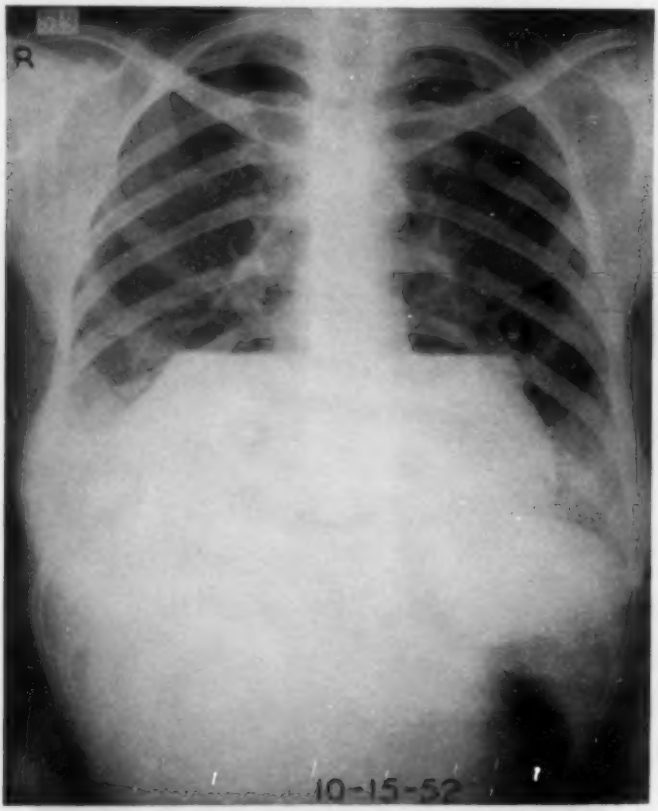

FIG. 4. Roentgenogram taken after the aspiration of 800 c.c. of fluid and the replacement of 200 c.c. of air. A definite fluid level is seen bilaterally.

This case was presented at the weekly conference of the staff of the Department of Internal Medicine, and it was the consensus that this was a large mediastinal cyst rather than a chronic pericardial effusion. Members of the Thoracic Surgery Staff concurred in this opinion, and thoracotomy was advised.

The operation was performed on October 24, 1952. With the patient lying in the supine position the incision was begun in the right midaxillary line, carried transversely beneath the right breast and across the sternum to the left midclavicular

line at the level of the fifth intercostal space. The right pleural cavity was entered through the fifth intercostal space and the sternum was divided transversely at this level. The left fifth interspace was opened parasternally for a distance of 8 cm.; however, the parietal pleura was not incised. A huge cyst was encountered (figure 5) in the anterior mediastinum and extrapleural space, encroaching upon the right pleural space anterior, lateral and posterior to the right lower and middle lobes. It compressed these portions of the right lung. It was adherent by friable adhesions to the anterior and lateral surfaces of the pericardium on the right, but there was no

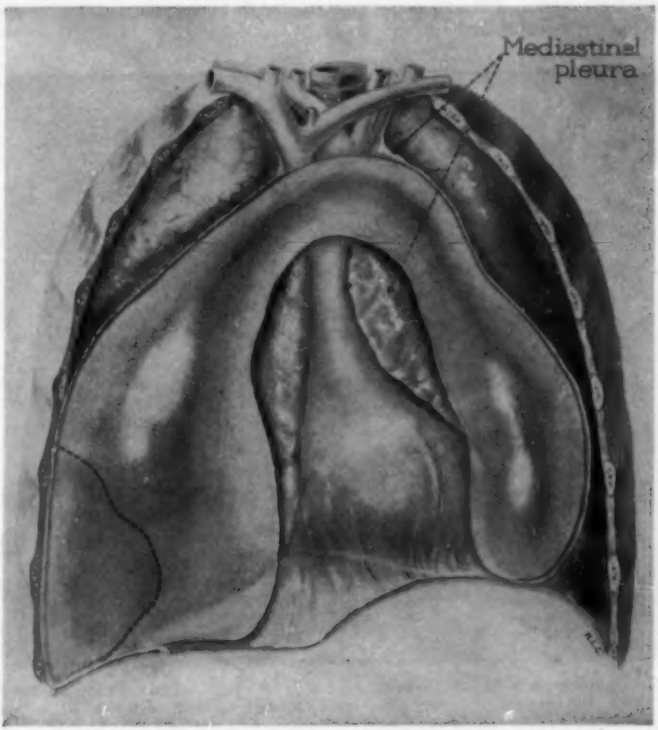

FIG. 5. Semidiagrammatic drawing of the pericardial cyst in situ. Dotted line at reader's left indicates the lateral and posterior extension of the cyst. Note that the cyst is entirely extrapleural.

pedicle to the pericardium and no communication with the pericardium. It was an inverted U-shaped structure, the arch of which lay anterior to the base of the pericardium. It impinged upon the left pleural space, compressing the anterior medial portion of the left lung. The wall of the sac was thin and translucent, so that the air and fluid within the sac were readily visible. The right portion of the filled sac measured 26 by 13 by 16 cm. and the left part 23 by 8.5 by 8 cm. A small opening was made in the sac and 900 c.c. of clear, straw-colored fluid were aspirated, together with the air which had been placed in the cyst before the operation. The cyst wall

and mediastinal pleura were densely adherent to the right phrenic nerve, which was preserved only by careful dissection. The left portion of the cyst was separated from the pericardium and mediastinal pleura with ease, making it unnecessary to enter the left pleural cavity.

Grossly, the pericardial cyst consisted of an hour-glass sac, the neck having a diameter of 2 cm. The cyst wall was thin and translucent in some areas, while in others it was thicker and opaque. The outer surface was relatively smooth but the inner surface had numerous folds of the cyst wall (figure 6). The microscopic description was as follows: "This is a cyst lined with flattened cells presumably mesothelial in origin. Fibrous adhesions are present over the surface of the cyst. There is no evidence of malignancy."

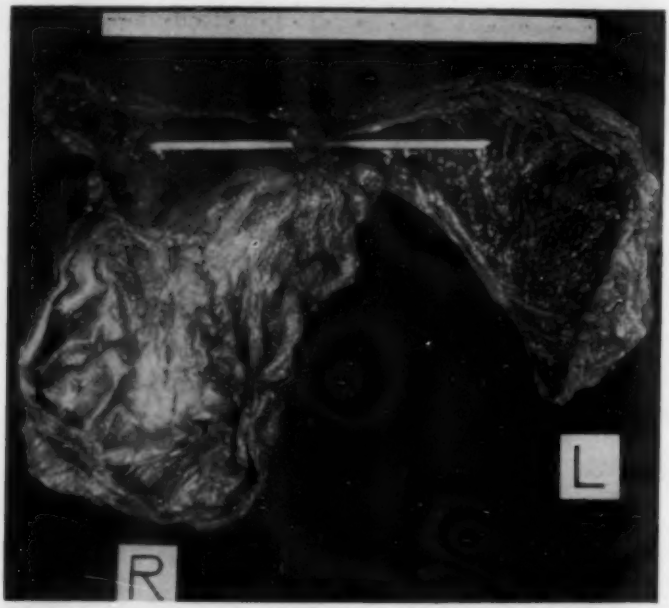

FIG. 6. Photograph of the pericardial cyst after it was opened. Probe is located in the connection between the right and left portions of the cyst.

The patient's postoperative course was uneventful and she was discharged on the seventh postoperative day. X-ray of the chest taken on the sixth postoperative day showed the abnormal shadow to be no longer present and evidence of pleural reaction in the right costophrenic angle.

DISCUSSION

The presence of an inverted U-shaped pericardial coelomic cyst straddling the heart in the manner described has not been recorded previously, although Lillie et al.[1] reported a case in which the cyst was found "beneath the anterior mediastinal pleura attached to the upper one-third of the pericardium and extending anteriorly in front of the arch of the aorta and slightly to the left of the

thoracic cavity." The embryologic significance of this cyst is that it is probably the persistence of one of the lacunae which is present ventral to the primitive streak (figure 7). Normally the lateral and ventral lacunae fuse to form the pericardial coelom [4]; however, it would appear that in this case one of the ventral lacunae did not fuse with the others, and thus persisted as a cyst in the midline and gradually enlarged and extended down both sides of the heart.

Pericardial cysts are most often located in the anterior mediastinum at the cardiophrenic angles. The thin translucent walls of these cysts consist of fibrous connective tissue lined by a single layer of mesothelial cells. The cyst fluid is a clear, straw-colored transudate.

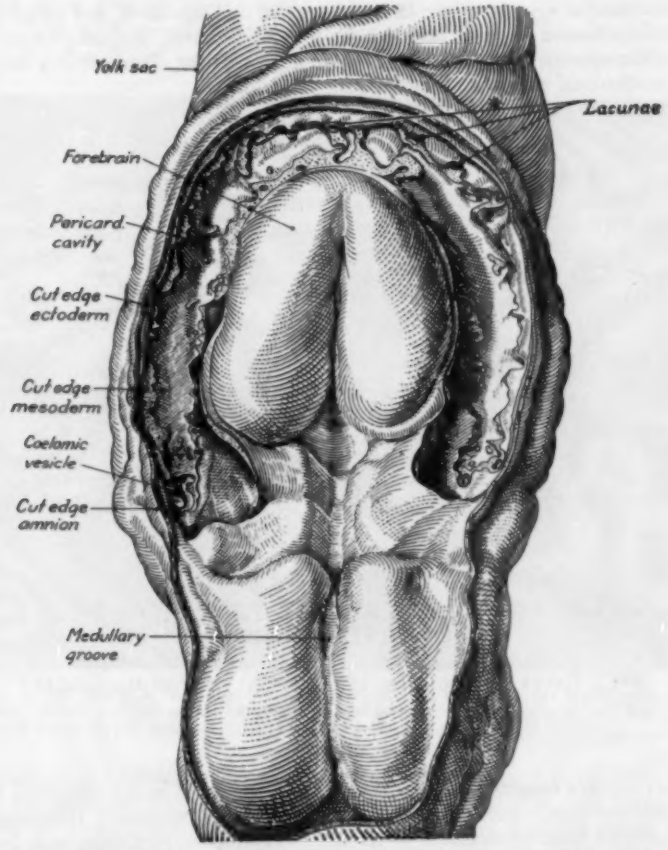

FIG. 7. Dorsal view of plaster model of embryo. Pericardial cavity is being formed by the fusion of discrete coelomic vesicles (lacunae).

[4] Persistence of a ventral lacuna is the probable source of the pericardial cyst being reported (Davis, C. L.[4]).

The lesions usually considered in the differential diagnosis of pericardial cysts include dermoid cysts, hernia through the space of Morgagni, thymoma, bronchogenic carcinoma, lipoma, pericardial fat pad, loculated pericardial effusion, or diverticulum of the pericardium. Seldom is chronic pericardial effusion confused with such cysts. However, one can readily realize after inspecting the x-rays that it would be difficult, from the x-rays alone, to differentiate chronic pericardial effusion from this unusually shaped pericardial cyst. Nevertheless, the definite pulsations seen at the borders of the mass on fluoroscopy and the definite areas of translucency just to the right of the lower thoracic spine (figure 2) suggested that this was not a homogeneous mass of fluid within the pericardium, but rather a peculiarly shaped mediastinal cyst. It was because of these features and the equivocal cardiac symptoms, the lack of the usual findings associated with chronic pericardial effusion, such as high venous pressure, ascites, dyspnea, edema, etc., and the low specific gravity of the aspirated fluid, that the diagnosis of a huge anterior mediastinal cyst was considered the most likely.

Summary

A report of a peculiarly shaped pericardial cyst has been presented. A chronic pericardial effusion was considered as a possibility in the differential diagnosis but was rejected before operation for reasons mentioned. This is the largest pericardial cyst reported in the literature and the only one with this unusual configuration. The embryologic significance of this cyst is discussed.

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AMYOPLASIA CONGENITA: CASE REPORT AND REVIEW OF LITERATURE*

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I. Introduction

Amyoplasia congenita is a condition rarely reported in the American literature, only three such references being found.[1, 2, 3] Approximately 100 cases have been collected from the available American and European literature, with the possibility of duplication in some reports. The condition, which has also been called dysmyoplasia congenita, multiple articular rigidity, arthrogryposis multiplex con-

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genita, and myodystrophia fetalis deformans, was first described by A. G. Otto [4] in 1841. However, it remained for Rosenkranz [5] in 1905 and Rocher [6] in 1913 to present sizable collections of cases and for Sheldon [7] in 1932 to give a comprehensive discussion. This case is presented as a reminder of the existence of the disease and as an unusually mild form, only the upper extremities being involved and causing little disability. It is also interesting in that a similar, although even milder, disturbance probably was present in a brother. Familial incidence is hitherto unreported, to our knowledge.

II. Clinical Features

The usual findings in the disease were well described by Sheldon.[7] He stated: "The characteristic features [consist] of immobility of one or more joints, generally symmetrical in distribution and dating from intrauterine life. The

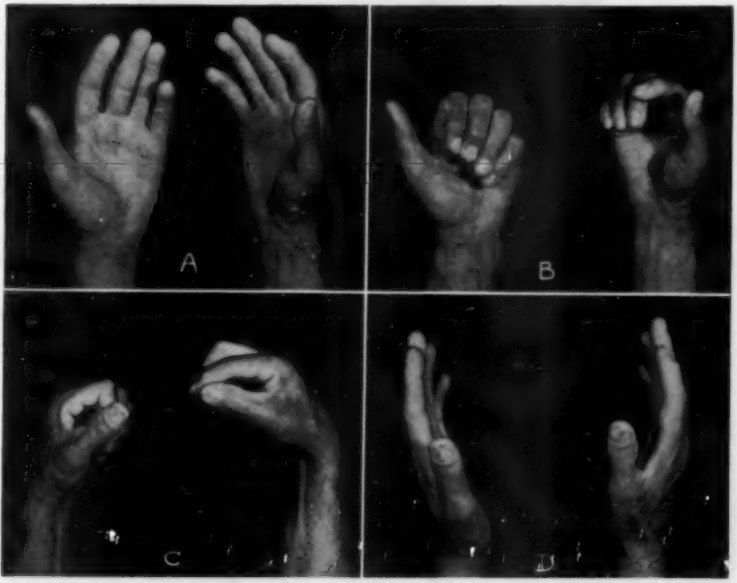

Fig. 1. Photographs showing diminished flexibility of joints of upper extremities. A. Elbows flexed and full supination, digits in full extension. B. Digits in full flexion. C. Digits and wrists in full flexion. D. Digits and wrists in full extension.

immobility may be absolute, or movement may be severely limited. The fixation of the joints has the clinical appearance of fibrous ankylosis, but there is no evidence of inflammatory change to account for this and it would appear more probable that the condition depends primarily upon some developmental defect. In this connection, the incomplete development, or even entire failure of development, of certain groups of muscles in the limbs, which has been recorded in cases specifically examined from this point of view, has been a striking feature." Posi-

tion of the extremities may vary considerably in different patients. Brandt [5] stated that the joints were usually fixed with forearms pronated, elbows and knees extended, feet in varus position to the extent that the patient may stand on the backs of the feet, and fingers flexed with flexion and ulnar deviation at the wrists. Rocher [6] mentioned that there may also be stiffness of the spine and jaws. There is great diminution of some muscle groups and complete absence of others.[7] Complete ankylosis is rare; some passive motion is usually possible.

FIG. 2. Roentgenograms demonstrating absence of bony change in spite of clinical impression of ankylosis. A. Hands and wrists. B. Left elbow. C. Right elbow. Bone change in interphalangeal joints of right index finger due to old fracture.

The disease is sometimes a rapidly progressive degeneration in muscle groups involved at birth, but does not spread to other, originally uninvolved muscle groups. Even in intrauterine life the joints are usually affected, fetal movement generally being weak.[8]

Anatomic anomalies in these patients may occur. These include webbing, hyperostosis frontalis interna, urachus abnormalities, undescended testicles, inguinal hernia and cleft palate.[2, 8] Intellect is unimpaired by the disease.

Case Report

A 46 year old white American male was seen for a welfare agency on May 1, 1953, for evaluation of disability. He complained largely of symptoms characteristic of the spastic colon syndrome; stiffness of his hands, wrists and elbows was discovered only incidentally. He stated that his parents had told him his thumbs had always been stiff, but he thought his fingers became stiff during adolescence, not recalling earlier disability such as difficulty in play. He said he had been hard of hearing for many years without apparent cause. The right index finger had been injured in a mill accident in 1948, being fractured and lacerated, and the finger since had been much stiffer. Family history indicated that a brother, aged 38, had always had similar but less severe stiffness in the right hand; however, it was so little disabling he was drafted in World War II. The patient had been able to do farm and saw mill work satisfactorily during most of his adult life.

Except for slightly diminished hearing, physical examination yielded abnormal results in only the upper extremities. In the elbows, wrists and digits there was moderate to marked limitation of motion, both active and passive, and with little difference in the two. Supination of the right forearm was limited to approximately 50 per cent, and there was less limitation of the left. Muscular development in the forearms was apparently normal. The skin of the hands was somewhat shiny and inelastic but of normal color and temperature. There was a half-inch scar on the palmar surface of the right index finger, over the proximal interphalangeal joint. There was moderate atrophy or poor development of the intrinsic muscles of both hands. There was almost no flexion of the left wrist and approximately 50 per cent limitation of flexion of the right wrist; extension of either wrist was negligible. Flexion of the fingers of the left hand was limited approximately 50 per cent and of the right hand about 75 per cent. (The previously fractured and lacerated right index finger was firmly ankylosed at the proximal interphalangeal joint.) The full extent of motion of these joints is shown in the photographs in figure 1. There was good power in the grip bilaterally, despite the inability to close the hand tightly.

Routine laboratory tests, including urinalysis, complete blood count, and blood Mazzini and Venereal Disease Research Laboratory Tests, gave normal results throughout. X-ray examination of the elbows and hands revealed bony ankylosis between the proximal and middle phalanges of the right index finger, with marked arthritic changes about the joint between the middle and distal phalanges. No other bony change was seen. These largely normal roentgenologic findings are demonstrated in figure 2.

Comment: This man was first thought to have multiple articular ankyloses. However, x-ray examination was entirely within normal limits except for the site of an old fracture, placing the case in the category of amyoplasia congenita.

III. Pathology

Histologically, Brandt [8] reported that biopsy of an involved quadriceps muscle revealed increased interfascicular connective tissue, extreme atrophy of muscle cells with nuclear proliferation, and degenerative changes in the peripheral motor neurone. Examination at necropsy revealed granular or vacuolar degeneration of the anterior horn cells of the spinal cord, with disappearance of motor cells, extreme chromophilia and cell sclerosis, and minor changes in the facial nerve nucleus and the nucleus of the spinal accessory nerve.

IV. Etiology

Rocher [6] attempted to distinguish between primarily muscular or primarily nervous origin of the disease by observing muscular response to electrical stimulation. He reported: "The muscles never show a reaction of degeneration, so the muscular atrophy is probably not of nervous origin, but the reactions of faradism or galvanism are diminished or absent, indicating hypoplasia or aplasia of muscle." Sheldon [7] also felt that the disease was primarily a muscle aplasia, while Middleton [9] was of the opinion that the cause of the disorder was fatty degeneration of muscles in intrauterine life analogous to muscular dystrophies of later life. Gilmore [10] and Brandt,[5] on the other hand, felt that it was a neurologic disease related to amyotonia congenita and the progressive muscular atrophy of Werdnig and Hoffmann, the differences "explained by differences in time, intensity and duration of application of a single etiological agent . . . the primary abnormality (probably lying) in the motor nerve endings." [10] Gilmore [10] also was of the opinion that the semi-rigidity of the joints was due to retraction of greatly atrophied muscles, while Sheldon [7] thought the action of preserved antagonists may be the cause of the immobility. Stern [1] believed the rigidity to be due to periarticular thickening, possibly as a result of intrauterine inflammation of the joints.

Familial incidence of the condition has not been reported, although other abnormalities in siblings such as meningocele and cleft palate have occurred.[11] Hillman and Johnson reported two sets of monozygotic twins, each with one normal and one with amyoplasia, and were unable to offer a theory as to the cause on a basis either of heredity or of intrauterine influences. However, a condition in sheep closely resembling the disease in man has been described which seems definitely to be a recessive hereditary trait.[12] This may be the way in which the probably related conditions, amyotonia congenita and progressive spinal muscular atrophy, are transmitted.[13] In such a rare condition as amyoplasia it is difficult to find enough cases to attempt a "family tree" study. Brandt [5] noted that amniotic fluid was usually scanty and breech presentations were common, possibly pointing to an obstetric abnormality as contributing to the cause.

V. Therapy

Treatment of the condition is largely orthopedic, consisting of manipulations (sometimes under anesthesia), temporary fixation in overcorrected positions, and surgery such as fasciculotomy, capsulotomy, tenotomy, open reduction of hip joints and arthrodesis for clubfoot.[2, 5]

Summary

1. An unusually mild case of amyoplasia congenita in an adult is presented. The possibility of familial incidence, hitherto unreported, is mentioned.

2. The literature concerning this rather rare condition is reviewed.

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CORTISONE AND THE TREATMENT OF HEAT STROKE*

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THE antipyretic and hypothermic effects of corticotropin and cortisone are well documented. Kass and Finland [1] showed that the febrile response to injections of typhoid bacilli and influenza virus could be lessened by corticotropin. Douglas and Paton [2] demonstrated that corticotropin reduced the temperature both in normal animals and in experimental pyrexia. Therapeutically, adrenocortical hormones have been used to alleviate the pyrexia and toxemia of pneumonia,[3] typhoid fever,[4, 5] Rocky Mountain spotted fever [6] and generalized peritonitis.[7]

Ingraham, Matson and McLaurin [8] suggested that corticotropin and cortisone might help prevent the hyperthermia of hypothalamic damage which sometimes results from surgery for craniopharyngiomas. They observed six cases in which postoperative hyperthermia was not noted after preparation of their patients with cortisone or corticotropin.

Heat stroke or heat pyrexia is a grave, often fatal disease. Fundamentally, heat pyrexia involves a failure of the neurogenic mechanism of sweating. In view of the well known antipyretic properties of cortisone, and the thesis of Ingraham, Matson and McLaurin that cortisone may prevent the hyperthermia of hypothalamic injury, it appeared of theoretic and therapeutic interest to determine if cortisone would manifest its antipyretic effect in heat stroke.

CASE REPORT

A 25 year old white man was admitted to the hospital in August, 1953, because of hyperpyrexia. The patient had been exposed to a relatively hot, humid environment. Physical examination revealed a man in acute distress. The rectal temperature was 106.2° F.; the pulse, 100; the respirations, 32; arterial pressure, 130/60 mm. Hg. The skin was flushed, hot and dry, without a sign of hidrosis. The cardiac sounds were forceful. The remainder of the physical findings were noncontributory.

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A diagnosis of heat pyrexia was made and therapy was immediately instituted by means of continued evaporative cooling. The patient's temperature declined but remained moderately elevated.

One hundred milligrams of cortisone were then administered by mouth at six hour intervals for three doses. Then, 50 mg. of cortisone were given orally at six hour intervals for 24 hours. Following this, three 25 mg. doses of cortisone were administered eight hours apart and, in the next 24 hours, 25 mg. of cortisone were given twice. During this trial of oral cortisone, evaporative cooling was maintained.

Despite the administration of cortisone the patient's temperature remained moderately elevated without a sign of sensible perspiration. Figure 1 illustrates the rectal temperature of the patient during the trial of cortisone. After the administration of cortisone was discontinued there was no exacerbation of the pyrexia.

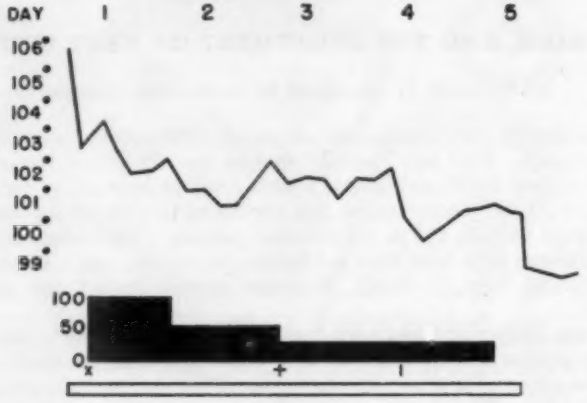

FIG. 1. The temperature in a case of heat pyrexia, showing the ineffectiveness of cortisone as an antipyretic in this disease. Evaporative cooling was instituted before and continued throughout the period of cortisone administration. ■—Mg. of cortisone at °6, °8, and |12 hr. intervals. □—Evaporative cooling.

Approximately sixteen and one half hours after the last oral dose of cortisone, and four and one quarter days after the institution of cortisone therapy, hidrosis appeared and the patient's fever disappeared by crisis. For the next several days the patient manifested impaired cerebration but then made an uneventful recovery.

DISCUSSION

It is noteworthy that orally administered cortisone had no apparent effect on this patient's heat pyrexia. In another (and personally observed) case of heat stroke, which was also treated by evaporative cooling, 100 mg. of cortisone given intravenously by infusion also were without effect on the hyperpyrexia or anhidrosis. These findings contrast with the useful antipyretic effects of short-term cortisone therapy in the febrile toxic state of typhoid fever [4, 5] and Rocky Mountain spotted fever.[6]

The above findings suggest that any beneficial effect of corticotropin or of cortisone when used as an adjunct to the surgery of craniopharyngiomas may be

due to the prevention of pituitary-adrenal collapse and not to an antagonism of hypothalamic injury, as suggested by Ingraham and co-workers.[8]

The method of choice in the treatment of heat pyrexia remains that of prompt cold hydrotherapy. Although textbooks of medicine by Christian,[9] Yater [10] and Barr and Musser [11] recommend evaporative means of cooling, the experimental work of Daily and Harrison [12] has clearly shown the superior value of ice-cold hydrotherapy.

Summary and Conclusion

Orally administered cortisone in one case and parenterally administered cortisone in another were without effect on either the hyperpyrexia or the anhidrosis of heat stroke.

Cortisone appears of no value as an antipyretic adjunct in the treatment of heat pyrexia.

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APLASTIC ANEMIA DURING THE TREATMENT OF HYPERTHYROIDISM WITH TAPAZOLE*

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SINCE the introduction of thiouracil for the treatment of hyperthyroidism there has been a constant search for more potent and less toxic antithyroid drugs. None of these drugs, however, is free from a variety of undesirable toxic side effects. At the present time propylthiouracil and Tapazole (1-methyl-2-mercaptoimidazole) are the drugs most frequently employed because of their proved efficacy and the relatively low incidence of toxic side reactions. Toxic reactions of all types with propylthiouracil have occurred in 1.6 to 3.2 per cent of cases.[1-4] Severe leukopenia and agranulocytosis have occurred in 0.5 to 1.0 per cent of patients,[2-9] and several fatalities from agranulocytosis have been reported.[7-9]

Tapazole has been recommended as the drug of choice in the treatment of hyperthyroidism because of its greater potency and lower incidence of toxic reactions compared to propylthiouracil.[10] However, Bartels[4] has reported 16 toxic reactions in the treatment of 214 patients with Tapazole, an incidence of 7.5 per cent. Several cases of severe granulocytopenia[4, 11, 12, 13] and two fatalities following the use of Tapazole have also been reported.[4]

The present report is that of a pregnant woman with hyperthyroidism who developed an aplastic anemia during treatment with Tapazole.

CASE REPORT

A 37 year old white married woman was admitted to the University Hospitals of Cleveland on January 19, 1953. She had been in good health until September, 1952, when she noted the onset of nervousness, palpitations, shortness of breath and insomnia. She was seen by her private physician at that time and was treated with barbiturates. The symptoms persisted and, in addition, she developed increasing fatigability and weight loss despite an excellent appetite. She was seen again by her physician on October 11, 1952. Examination showed the skin to be flushed, damp and smooth. There were slight prominence of the eyes, pronounced tremor of the hands, and diffuse enlargement of the thyroid gland. A basal metabolic rate was plus 43, I^{131} uptake over the thyroid gland was 75 per cent in two hours, and serum cholesterol was 191 mg. per 100 c.c. A white blood count was 7,100, and hemoglobin, 71 per cent. On October 18 the patient was started on propylthiouracil, 300 mg. daily. After 13 days there was a noticeable improvement. However, she developed a severe generalized urticaria and the propylthiouracil was stopped. She was treated with antihistamines for the urticaria, and on November 7 was started on Lugol's solution, 3 drops three times a day. At that time the white blood count was 6,400. On November 22 the patient reported that she had missed her menstrual period (expected November 11). A pelvic examination was suggestive of an early pregnancy, and a Friedman's test was positive. The Lugol's solution was continued until December 6, when the patient developed a macular rash on both thighs which had a lichenoid and scaly appearance. It was felt that this rash was due to a sensitivity to iodine, and the Lugol's solution was stopped. Tapazole, 5 mg. four times daily, was started. The white blood count at that time was 9,600,

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with a normal differential count. On December 22 the dose of Tapazole was increased to 40 mg. daily because of exacerbation of the symptoms of hyperthyroidism. This dose was maintained for about 10 days, at which time the patient reduced the dose of Tapazole to the initial dose of 20 mg. daily because she was "feeling better." The patient did not visit her physician from December 22, 1952, until the day of admission, January 19, 1953, in spite of instructions to return at weekly intervals. Four days prior to admission to the hospital she developed a sore throat, and three days before admission she noted the onset of painful ulcerated lesions on her tongue. She visited her physician, who found her to be febrile. A white blood count was 3,000, and the patient was admitted to the hospital.

The past history was significant in that in 1944 the patient had had recurrent urticaria of about one year's duration. There was then no apparent relation to drug ingestion or food allergy.

Physical examination on admission to the hospital revealed a moderately ill, anxious woman showing marked hyperactivity and complaining of a sore mouth. Her temperature was 38.4° C.; pulse rate, 110; respiratory rate, 24; and blood pressure, 130/68 mm. of Hg. There was a fine tremor of the hands. The skin was warm and dry, and no jaundice, petechiae or ecchymoses were noted. The eyes

TABLE 1

Serial Blood Counts on Patient

	Jan. 20	Jan. 22	Jan. 23	Jan. 24	Jan. 26	Jan. 27	Jan. 28	Jan. 30	Feb. 2
Hemoglobin, gm. per 100 c.c.	9.5	8.3	8.5	8.1	6.9		8.5	8.4	8.4
Red blood count × 10^6	3.75	2.86	3.13	3.07	2.80		4.22	3.50	3.54
White blood count	1,100	700	600	725	2,700		3,600	4,800	7,200
Hematocrit, %	28	25	26	24.5	22.0		30.0	30.0	30.0
Platelet count	122,000	131,240	120,000	104,000	158,000		295,000	Normal	Normal
Reticulocytes, %			0.5					2.8	
Segmented neutrophils, %				4	3		11	26	43
Unsegmented neutrophils, %					8		17	17	18
Metamyelocytes, %							4	3	
Eosinophils, %	9	7	5	1	1		1		
Basophils, %									
Lymphocytes, %	85	90	90	82	29		12	18	18
Atypical lymphocytes, %					44		46	31	16
Monocytes, %	6	3	5	12	7		5	5	5
Immature monocytes, %					8		4		

Transfusion 500 c.c. whole blood

showed widened palpebral fissures without definite exophthalmos. There were numerous small (1 to 2 mm.) ulcerations on the palate, buccal mucosa, tongue and gums. The ulcers had a white necrotic base with a surrounding zone of erythema. Several enlarged, tender submaxillary lymph nodes were palpated at the angles of the jaw bilaterally. The thyroid gland was diffusely enlarged to about two to three times normal size, and was moderately soft and without nodulation. The lungs were clear. The heart was not enlarged, and a moderately soft systolic murmur was heard over the pulmonic area. The liver and spleen were not palpable. The uterine fundus could not be felt by abdominal palpation. Pelvic and rectal examinations were not done at this time. The remainder of the physical examination was essentially negative.

Peripheral blood studies (table 1) on the morning following admission to the hospital showed the following: hemoglobin, 9.5 gm. per 100 c.c.; red blood count, 3,750,000; hematocrit, 28 per cent. The white blood count was 1,100, with a differential count of lymphocytes, 85 per cent; eosinophils, 9 per cent, and monocytes, 6 per cent. The platelet count was 122,000; the bleeding time, clotting time and clot retraction were normal. The urine was normal; fasting blood sugar, 85 mg. per 100 c.c.; serum cholesterol, 180 mg. per 100 c.c. An x-ray of the chest was normal, and an electrocardiogram showed a normal record with a sinus tachycardia.

Serum bilirubin was 0.5 mg. per 100 c.c. direct, and 2.6 mg. per 100 c.c. total. A sternal bone marrow aspiration on the second hospital day showed almost complete acellularity of the marrow. A nucleated cell count was only 3,500 per cubic millimeter. The granulocytic series was absent except for a rare eosinophil and eosinophilic myelocyte. A rare normoblast was seen; no megakaryocytes were present. The majority of the cells were mature lymphocytes, and immature and abnormal forms were present. A bone marrow aspiration from the iliac crest on the following day showed the same degree of hypocellularity and distribution of cells.

Hospital Course: On admission to the hospital the patient was started on penicillin and streptomycin for control of infection, and saturated solution of potassium iodide, one drop daily, for her hyperthyroidism. After three days on this régime her temperature remained elevated to 38.5° C., and there was progression of the mucosal ulceration. The white blood count fell to 600 per cubic millimeter, the platelet count to 104,000, and the hematocrit to 26 per cent. At this time oral cortisone therapy was begun. The initial dose, 300 mg. per day, was gradually reduced to 100 mg. per day by the sixth hospital day, and was continued until shortly before discharge. On the day following the start of cortisone therapy the temperature fell to normal and remained so for the remainder of the hospital course. The white blood count, 600 per cubic millimeter at the start of cortisone therapy, gradually began to rise, with the concomitant appearance of polymorphonuclear neutrophils in the peripheral blood (table 1). By the thirteenth hospital day the white blood count was 7,200 per cubic millimeter, with 43 per cent neutrophils. The platelets also increased in number following the onset of cortisone therapy, and in five days returned to normal levels of 250,000 per cubic millimeter. The red blood count, hemoglobin and hematocrit continued to fall after cortisone was started. By the eighth hospital day the red blood count fell to 2,600,000, hemoglobin to 7.0 gm. and hematocrit to 22 per cent. At this time the patient was transfused with 500 c.c. of stored whole blood, following which the red blood count rose to 3,550,000, the hemoglobin to 8.5 gm. and the hematocrit to 30 per cent. The hematocrit remained at about 30 per cent for the remainder of the hospital course. On the day cortisone therapy was begun the serum bilirubin was 0.5 mg. direct and 2.6 mg. total. At this time both fecal and urinary urobilinogen were reported as being increased. All liver function studies were normal, and at no time was clinical icterus noted. A direct Coombs' test was negative. Four days after cortisone therapy was started the serum bilirubin fell to 0.5 mg. direct and 1.4 total; three days later the serum bilirubin had returned to normal values of 0.2 mg. direct and 0.5 mg. total. With the improvement in the peripheral blood counts and blood chemistry there were marked symptomatic improvement and complete healing of the mucosal ulceration.

On the eleventh hospital day, after the white blood count and platelet counts had returned to normal and the red blood counts had stabilized, a repeat sternal marrow aspiration was done. Although both smears and fixed tissue sections made from bone marrow particles still showed hypoactivity of the marrow, erythroid, myeloid and megakaryocytic elements were present. The patient was discharged from the hospital on the twentieth hospital day, after both cortisone and antibiotics had been stopped for at least five days. At the time of discharge the white blood count and platelet count were normal and the hematocrit was 30 per cent.

Discussion

The patient in this report had agranulocytosis, anemia and thrombocytopenia on admission to the hospital. Bone marrow studies showed extremely low

nucleated cell counts and almost complete absence of myeloid elements in two consecutive bone marrow aspirations from two different locations. Although estimation of bone marrow activity based on the cellularity of smears made from marrow aspiration is not always reliable,[14] the peripheral blood and marrow findings in this patient are compatible with the diagnosis of aplastic anemia. In addition, the rapid fall in red blood counts and elevated indirect serum bilirubin, in the absence of other evidence of liver disease, indicate the presence of a hemolytic component in this patient's anemia.

Rapid clinical and hematologic improvement followed the onset of cortisone therapy in this patient. The role of cortisone and ACTH in the therapy of drug-induced agranulocytosis and aplastic anemia has not been definitely established. Cortisone has been shown to have a deleterious effect on bone marrow regeneration following irradiation,[15] and also to increase the leukopenia following nitrogen mustard therapy in animals.[16] On the other hand, several cases of rapid and dramatic improvement of drug-induced agranulocytosis with cortisone and ACTH therapy have been reported.[17-19]

The prognosis in drug-induced aplastic anemia is serious. A significant number of patients, however, recover on conservative therapy alone, with the use of antibiotics and blood transfusions as needed. About 50 per cent of patients who developed aplastic anemia from chloramphenicol therapy recovered.[20] It is possible that this patient may have recovered without the use of cortisone. However, the rapid and dramatic clinical improvement following the institution of cortisone therapy suggests that cortisone may have hastened her recovery.

Conclusions

1. A case is reported of aplastic anemia occurring during Tapazole therapy in which cortisone appeared to hasten recovery.

2. The role of cortisone in the therapy of drug-induced agranulocytosis and aplastic anemia is discussed.

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EDITORIAL

HEREDITARY HEMOGLOBINOPATHIES

In 1923 Taliaferro and Huck [1] proposed the theory that sickle cell disease, first described by Herrick [2] in 1910, was due to the inheritance of an abnormal gene which behaved as a Mendelian dominant characteristic. Clinical variation in severity, characterized as sicklemia (sickle cell trait) and sickle cell anemia respectively, was believed due to a difference in penetrance or expression of the abnormal gene. In vitro demonstration of sickling by exposure of erythrocytes to reduced oxygen tension, does not permit differentiation of the two clinical states. In 1940 Sherman [3] noted that a considerably greater reduction in oxygen tension was required to induce sickling of trait erythrocytes as compared to those from patients with the active disease. It was also observed that 30 to 60% of the erythrocytes in the venous blood of patients with sickle cell anemia were more or less constantly sickled in vivo as compared to 1% or less in patients with the trait. No specific reason for these differences was known.

In 1949, Neel [4] proposed a new genetic theory to explain the clinical and hematological differences between sicklemia and sickle cell anemia. It was postulated that the abnormal gene might occur in a homozygous state, i.e., inherited from both parents, in which case the individual would develop sickle cell anemia. If, however, only one abnormal gene was inherited and the corresponding gene from the other parent was normal, i.e., a heterozygous state, the resultant picture would be that of sicklemia. Support for this theory appeared promptly in the form of a paper by Pauling et al.[5] on an electrophoretic study of normal hemoglobin and hemoglobin derived from patients with sicklemia and sickle cell anemia. Under suitable physical conditions, normal hemoglobin was observed to migrate toward the anode, while sickle cell hemoglobin migrated toward the cathode. Hemoglobin solutions prepared from individuals with sicklemia displayed two components, one with the electrophoretic mobility characteristics of normal hemoglobin, the other resembling sickle cell hemoglobin. Additional studies indicated that the heme moieties of the two hemoglobins were similar and that the difference apparently resided in the globin fraction of the molecule.

A series of investigations stemming from these basic reports has resulted in the development of the concept that a genetically controlled molecular

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abnormality in a single protein, in this instance hemoglobin, could be the underlying factor in the complex sequence of events characterizing various disease entities. For this group of disorders the generic term, hereditary hemoglobinopathies, has been proposed.[6] A brief review of some recent studies in this area will be presented.

For many years it has been known that the hemoglobin of the red cell of the fetus is chemically different from that of adult red blood cells. Although it is possible under suitable electrophoretic conditions to demonstrate differing mobilities for these two types of hemoglobin, a more common method of differentiation is that based on resistance to alkali denaturation. Fetal hemoglobin shows a greater resistance to alkali denaturation. It has been demonstrated[7] that about midway in gestation approximately 6 to 7% of the hemoglobin is of the normal adult (A) variety while the remainder (93 to 94%) is of the fetal (F) type. At birth 55 to 98% is still of the F type, but by two months of age this amount drops to approximately 46%, and at four months to about 10 to 12%. At the end of the first year of life virtually all of the hemoglobin is of the A variety. Small amounts (1 to 2%) of F hemoglobin have been found to be present later in life in a variety of chronic anemias. The exact significance of this observation is not known at present. It is of interest to note that some cases of sickle cell anemia have been demonstrated to have as much as 25% alkali resistant hemoglobin, presumably identical with F hemoglobin, but no correlation has been found between this or lesser amounts and the severity of the disease process.[8]

Of perhaps greater interest has been the recent observation that 40 to 60% of the hemoglobin in thalassemia major is of the F type.[8, 9] The erythrocytes in this disease are regularly characterized by a marked deficiency in hemoglobin. Despite the erythroid hyperplasia noted in the bone marrow in Mediterranean anemia the rate of maturation and release of red cells seems to be quite low. Rich[10] has suggested that the primary genetic defect in thalassemia is a block in the synthesis of normal (A) hemoglobin. The high proportion of F hemoglobin is looked upon as a compensatory continuation of an embryonic or fetal mechanism. Further investigations are obviously indicated in this area.

In the course of his investigations of hemoglobin from individuals with sicklemia, Pauling noted variation in the ratio of sickle (S) hemoglobin to A hemoglobin in different individuals with the trait. The amount of S

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hemoglobin varied from 22 to 50%. Wells and Itano [11] pursued this aspect of the problem further and found that the proportion of S hemoglobin was constant in affected individuals in a given family. The latter has recently proposed [12] the hypothesis that the rate of production of hemoglobin normally is also subject to genetic control. Three normal alleles, i.e., interchangeable genes, govern the rate of production. Therefore the ratio of A to S hemoglobin in individuals with sicklemia varies according to which of the normal alleles co-exists with the aberrant gene for sickle hemoglobin.

The verification of Neel's hypothesis regarding the genetics of sickle cell disease required the regular demonstration of sickling in both parents of a patient with sickle cell anemia. Such verification occurred, but in the process of family study exceptions were found in which only one parent exhibited sickling. Neel and Itano [13] carried out electrophoretic studies on the hemoglobin of the non-sickling parent and discovered a new variety of hemoglobin with an even lower electrophoretic mobility than hemoglobin S. This type has been since designated hemoglobin C. [14] The mutant gene responsible for this type of hemoglobin is apparently confined to Negroes. It is believed, however, not to be an allele of the gene responsible for sickling. Hemoglobin C has been found in combination with hemoglobin S (Sickle cell-Hemoglobin C disease), in combination with normal hemoglobin (Hemoglobin C trait), and as the only hemoglobin present (Homozygous hemoglobin C disease). The clinical and hematological characteristics of these entities will be discussed below.

Further family studies of individuals exhibiting sickling led to the discovery of a third abnormal type of hemoglobin, now designated as D, which has the same electrophoretic mobility as hemoglobin S but differs from it in its greater solubility.[15] To date only two instances of hemoglobin D trait have been reported. The individuals were white siblings described in the report of Itano. Clinical and hematological details have not been given.

From time to time in previous years the occurrence of chronic hemolytic anemia with a positive test for sickling in a Caucasian individual has been described. Critical review of such cases has revealed that most of the patients have been of either Sicilian, Italian, or Greek derivation. In 1945 Silvestroni and Bianco [16] described such a case and suggested that the disease was due to the inheritance of the gene for sickling and the gene responsible

[11] Wells, I. C., and Itano, H. A.: Ratio of sickle cell anemia hemoglobin to normal hemoglobin in sicklemics, J. Biol. Chem. **188**: 65, 1951.

[12] Itano, H. A.: Qualitative and quantitative control of adult hemoglobin synthesis. A multiple allele hypothesis, Am. J. Hum. Genet. **5**: 34, 1953.

[13] Itano, H. A., and Neel, J. V.: A new inherited abnormality of human hemoglobin, Proc. Nat. Acad. Sc. **36**: 613, 1951.

[14] Statement concerning a system of nomenclature for the varieties of human hemoglobin, Blood **8**: 386, 1953.

[15] Itano, H. A.: A third abnormal hemoglobin associated with hereditary hemolytic anemia, Proc. Nat. Acad. Sc. **37**: 775, 1951.

[16] Silvestroni, E., and Bianco, I.: Micro-drepanocito-anemia in un soggetto di razza bianco, Boll. Atti. Accad. Med. Roma **70**: 347, 1945.

for thalassemia. They proposed the name, microdrepanocytic anemia, for this disease. Neel et al.[17] believe that microdrepanocytic anemia, or sickle cell-thalassemia, is the entity most often responsible for sickle cell disease in Caucasians. In the red cells of four patients these investigators found 61 to 84% hemoglobin S and significantly increased amounts of alkali resistant (F) hemoglobin. Some 19 families presenting this disease have now been reported from Italy, the United States, and South America.

Although originally investigated by the use of the Tiselius electrophoresis apparatus, recent studies of the hereditary hemoglobinopathies have been greatly facilitated by the use of the technic of paper electrophoresis which, because of relative simplicity and rapidity of determinations, permits widespread clinical application. This technic, developed by Durrum in 1950,[18] permits separation of the various components of a protein solution by determining their mobility under the influence of an electric current for a given period of time through strips of filter paper saturated by buffer solutions of differing pH. In 1952, a modification of the technic of paper electrophoresis was reported by Kunkel and Tiselius.[19] Spaet first reported the application of Durrum's technic to the study of hemoglobin solutions.[20] In natural or artificial mixtures normal hemoglobin (A) is found to travel furthest from the point of origin toward the anode. Hemoglobin S travels somewhat slower and hemoglobin C slowest of all. Hemoglobin D cannot be differentiated by this method.

Utilizing the Kunkel-Tiselius apparatus, Smith and Conley[21] studied the hemoglobin in 500 Negroes chosen at random. An incidence of sickle cell anemia of 1% was found; sicklemia occurred with a frequency of 7.2%; sickle cell-hemoglobin C mixtures were found in 0.2%; hemoglobin C trait (C-A) in 1.8%. No examples of homozygous C hemoglobinopathy were found in this group. Other studies seem to substantiate the observation that approximately 1 to 2% of American Negroes have hemoglobin C rather than hemoglobin A in their erythrocytes.[22] It is estimated that approximately one in five cases of sickle cell anemia may be in reality sickle cell-hemoglobin C disease. Additional studies are needed to clarify this point.

Neel et al.[23] have recently studied several families members of which

[17] Neel, J. V., Itano, H. A., and Lawrence, J. S.: Two cases of sickle cell disease presumably due to the combination of the genes for thalassemia and sickle cell hemoglobin, Blood **8**: 434, 1953.

[18] Durrum, E. L.: A microelectrophoretic and microiontophoretic technique, J. Am. Chem. Soc. **72**: 2943, 1950.

[19] Kunkel, H. G., and Tiselius, A.: Electrophoresis of proteins on filter paper, J. Gen. Physiol. **35**: 89, 1952.

[20] Spaet, T. H.: Identification of abnormal hemoglobins by means of paper electrophoresis, J. Lab. and Clin. Med. **41**: 161, 1953.

[21] Smith, E. W., and Conley, C. L.: Filter paper electrophoresis of human hemoglobins with special reference to the incidence and clinical significance of hemoglobin C, Bull. Johns Hopkins Hosp. **93**: 94, 1953.

[22] Neel, J. V.: Implications of some recent developments in hematological and serological genetics, Am. J. Hum. Genet. **6**: 208, 1954.

[23] Neel, J. V., Kaplan, E., and Zullzer, W. W.: Further studies on hemoglobin C. Parts I and II, Blood **8**: 724 and 735, 1953.

exhibit the hemoglobin C trait (C-A). They came to the conclusion that no serious hematological difficulties arise as a result of the presence of this abnormal hemoglobin. Red cell survival studies were normal in these individuals. An important, although not pathognomonic, clue to the presence of hemoglobin C is the observation of significant numbers of "target" cells in the blood smear. Hemoglobin C trait individuals in this study were found to have 3 to 33% "target" cells. Sickling does not occur.

Several recent papers discuss the clinical and hematologic aspects of sickle cell-hemoglobin C disease.[6, 23, 24, 25] In general these patients exhibit a mild to moderate chronic hemolytic anemia with rare hemolytic crises. A number of patients had recurrent bouts of arthralgia. A significant number had episodes of painless hematuria. Moderate hepatosplenomegaly was present in childhood and seemed to persist into adult life. Several patients showed progressive sclerosis and flattening of the head of the femur. Sickling could be demonstrated regularly. Blood bilirubin was usually normal or only slightly elevated. Forty to 85 per cent of the red cells in the blood smears were of the "target" type.

Thus far only a few examples of homozygous C hemoglobinopathy have been studied and reported.[24, 26] In general the characteristics are those of a mild hemolytic anemia with perhaps even less clinical disability than sickle cell-hemoglobin C disease. Sickling is, of course, absent, but a high proportion of "target" cells are found. Splenomegaly is present. Spaet et al., in one case, found diminished red cell survival.

Microdrepanocytic anemia, or sickle cell-thalassemia, is a disease of considerably greater severity. In this regard it probably ranks next to active sickle cell anemia. Although anemia may be only of moderate severity, recurrent crises of abdominal and osteo-articular pain may be, transiently, quite disabling. Splenomegaly is regularly present. Marked morphologic abnormalities of the red cells are observed and sickling is easily demonstrated.

The availability of more precise methods for the study of hereditary hemoglobinopathies has led to important additions to anthropologic knowledge. For example, recent studies have disclosed a high incidence of an anemia resembling thalassemia in Bangkok, Thailand.[27] A high incidence of sickling has been demonstrated in certain areas of Greece [28] and Southern India.[29] In both locales simultaneous study of the Rh blood types revealed

[24] Ranney, H. M., Larson, D. M., and McCormack, G. H., Jr.: Some clinical, biochemical, and genetic observations on hemoglobin C, J. Clin. Invest. **32**: 1277, 1953.

[25] Levin, W. C., Schneider, R. G., Cudd, J. A., and Johnson, J. E.: A family with homozygous hemoglobin C and sickle cell trait union: a clinical, hematological, and electrophoretic study, J. Lab. and Clin. Med. **42**: 918, 1953.

[26] Spaet, T. A., Alway, R. H., and Ward, G.: Homozygous type C hemoglobin, Pediatrics **12**: 483, 1953.

[27] Minnich, V., Supa Na-Nakorn, Soodsarkon Chongchareonsuk, Su-ed Kochaseni: Mediterranean anemia. A study of 32 cases in Thailand, Blood **9**: 1, 1954.

[28] Choremis, C., Ikin, E. W., Lehmann, H., Mourant, A. E., and Zannos, L.: Sickle cell trait and blood groups in Greece, Lancet **2**: 909, 1953.

[29] Lehmann, A., and Cutbush, M.: Sickle cell trait in southern India, Brit. M. J. **1**: 404, 1952.

a pattern distinctly unlike the Negroid which would seem to indicate that the sickling mutation was not associated with Negro admixture but arose de novo.

New physico-chemical methods and verifiable genetic hypotheses have jointly provided a tremendous impetus to the investigation of this previously imperfectly understood group of diseases. Space has not permitted reference to certain recent studies which cast new light on the pathological physiology of sickle cell disease. Thus far the new methods have failed to reveal any hemoglobin abnormality in congenital hemolytic jaundice and, the usually non-pathogenic, ovalocytosis. The possibility that the genetic defect in these disorders might be the result of the defective formation of stroma has been suggested but not proved. Further advances in knowledge of the metabolism of the erythrocyte should not be long in forthcoming.

MILTON S. SACKS, M.D.

REVIEWS

Medical Treatment of Disease. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D., M.A.C.P., Hon. F.R.C.P. (Can.), DALE G. FRIEND, A.B., M.S., M.D., F.A.C.P., and MAURICE A. SCHNITKER, B.S., M.D., F.A.C.P. 985 pages; 17.5 × 22 cm. Oxford University Press, New York. 1953. Price, $25.00.

This loose-leaf book constitutes the new Volume VIII of The Oxford Medicine. The authors are men of wide and varied experience: to quote from the introduction by Dr. Burgess Gordon, "Dr. Christian drew from his vast experience of academic and hospital medicine. Dr. Schnitker utilized the unusual opportunities of general practice to elucidate the value of the newer drugs and procedures. Close associations in pharmacology and clinical medicine enabled Dr. Friend to provide a happy balance of fundamental principles and practical applications in treatment. The manuscript was passed from one author to another for criticism and careful integration and was completed before Dr. Christian's untimely death."

This volume has many virtues. Unlike many available books on therapy it is a comfortable size to handle. The text has been kept to a reasonable length by the rightful omission of sections on diagnosis and etiology which too often clutter therapeutic texts. The print is delightfully easy on the eyes and the text for the most part is unusually readable and practical. New treatments are not included simply because they are new; in the authors' words, "the new must have been proved to be better than the old, or definitely valuable in addition to the old, before it is selected as a method recommended for use." A selected bibliography of recent publications is a useful feature.

The worst that can be said of this work is that a few sections are rather sketchy and there are some minor inconsistencies; for example, chloramphenicol on one page is regarded as "a most useful prophylactic agent for the suppression of those infections likely to cause rheumatic fever, glomerular nephritis, bacterial endocarditis, and so forth." On the next page it is more rationally advised that this drug "should not be used indiscriminately and probably should be reserved for patients with typhoid fever or infections that do not respond to other less toxic antibiotics." Again, in the section on constipation, the reader is left uncertain of the status of bran: "roughage diets, chiefly diets with much bran, may be injurious. In some, however, they do work well and should be used. The daily use of bran is not advised."

To secure this volume the initial outlay is great and will discourage many. The high price is no doubt due mainly to the unusually handsome, flexible leather binder with its well made loose-leaf device. Future supplementary or revised pages will cost approximately 2 cents per printed page. If the present standards are maintained, and if the text is kept properly up-to-date, this will be a useful though expensive service, of value to internist, practitioner and student alike.

H. J. L. M.

Fundamentals of Neuropathology. By WILLIAM BROOKS DUBLIN, M.D. 685 pages; 26 × 17.5 cm. Charles C Thomas, Springfield, Illinois. 1954. Price, $18.50.

Since the original monograph of Spielmeyer in 1921, a number of textbooks of neuropathology have appeared. Most of these have followed traditional concepts or have shown strength along anatomic or morphologic lines. Many texts have emphasized the degenerative diseases, congenital anomalies, or tumors. Some texts have contained both fact and fancy. Conflicts and confusion have occurred between texts. Neuropathology has thus become a bit mysterious, somewhat complex, and a difficult subject for both medical student and neurologist and particularly, the pathologist who has suffered from the complexity, the admixture of theory and fact plus an avalanche of anglicized or foreign words, plus even a few coined words.

The author of this latest addition to the neuropathologic literature is not a neurologist but a pathologist who has shown a particular aptitude for and who has engaged in the practice of neuropathology. One might agree with the author that "neuropathology in its most lucid and practical form is general pathology with adequately extended consideration of the nervous system." With this premise, he has produced in clear, concise, simple terms, and in a straightforward fashion, a treatise on the application of the usual diseases affecting mankind to the nervous system and, using familiar pathologic terms, he adequately describes, classifies, and catalogs these lesions. There is no confusion. Familiar pathologic terms are used instead of traditional foreign or coined words. The author's style is relaxed, original, and simple, yet inclusive, carrying an air of authority. There are certain components of classification which might impress one reader a bit more than the other; however, such concepts are far from being inaccurate.

The illustrations are an outstanding feature of the volume and correspond very closely to the text. They are realistically chosen and are of good quality. Proper emphasis is given to the important facets of neuropathology; the inflammatory diseases, diseases involving blood vessels, and certain metabolic conditions. A chapter on trauma is well illustrated but omits a discussion of uncinate hernia. Proper emphasis is given to tumors of the central nervous system which are very expertly presented. A realistic consideration is given to disorders of obscure nature where the literature contains more conjecture than fact. This section contains only about 20 pages. References are included, and are generally well selected. The inclusion of references in the English language almost exclusively should be welcomed by most physicians. The excellence of typographical work is clearly seen by an inspection of this volume. Both engravings and color prints are of excellent quality as is the type.

The volume is a departure from traditional neuropathology. It adequately demonstrates that neuropathology is nothing more complex than ordinary general pathology applied to a specific organ, the nervous system. All useless terms, complex concepts and traditional ideas have been translated into simple terms understandable by all. Medical students, neurologists, and particularly pathologists, should find this lucid inclusive volume a welcome aid in the study of neuropathology. One might recommend it highly and without reservation as one of the outstanding volumes in its field.

J. A. W.

The Autonomic Nervous System: Anatomy, Physiology and Surgical Application. 3rd Ed. By JAMES C. WHITE, M.D., REGINALD H. SMITHWICK, M.D., and FIORINDO A. SIMEONE, M.D. 569 pages; 16 × 24.5 cm. The Macmillan Company, New York, N. Y. 1952. Price, $12.00.

This volume contains many excellent features including: (a) an excellent historical review of knowledge of the involuntary nervous system, which includes the beginnings of surgical intervention; (b) anatomy of the autonomic nervous system; (c) fundamental arrangement of system as a whole. In addition, terminology is clarified—sympathetic-thoraco-lumbar outflow—(anterior roots); parasympathetic—(craniosacral division), as well as the concept of gray and white rami, etc. The peripheral autonomic plexuses are discussed in concise style.

A chapter is devoted to the general physiology, and to the pharmacology of the autonomic nervous system. The sympathomimetic agents and the parasympathomimetic agents are discussed from the clinical viewpoint. The mechanism of blocking agents is clearly stated.

An extremely practical chapter describes the methods and technic of study of the sympathetic nervous system.

Specific disease entities, including peripheral vascular disease, diseases of the extremities, disturbances of the head, brain, meninges and spinal cord are discussed, as well as diseases of the heart and aorta as related to the autonomic nerve system. In addition, diseases of the genitourinary and gastrointestinal tracts are discussed, as well as diseases of the lung. A chapter is devoted to the problem of hypertensive cardiovascular disease.

The technic of cervical, thoracic and abdominal sympathectomy is discussed and well illustrated.

This is a valuable reference book both for the busy general surgeon and for the individual seeing such problems only occasionally. The bibliography is excellent, and the cross indexing most satisfactory.

G. H. Y.

Peripheral Nerve Injuries: Principles of Diagnosis. 2nd Ed. By WEBB HAYMAKER, M.D., and BARNES WOODHALL, M.D. 333 pages; 16 × 24.5 cm. W. B. Saunders Co., Philadelphia. 1953. Price, $7.00.

Haymaker and Woodhall combined their experiences as Chief of Pathology and Chief of Neurosurgery in the U. S. Army Medical Corps during World War II to produce the first edition of *Peripheral Nerve Injuries.* Now a second edition has corrected the few minor objections to the original publication and has in addition, 47 new illustrations and a new chapter on "degrees of injury."

Peripheral Nerve Injuries is not just a good book, it is excellent. The well organized text is simple and yet inclusive. The illustrations are abundant and well selected. The reproduction of photographs is of the highest calibre. Indeed, this book is a rarity: a masterful example of the bookmaker's art on a subject well written by experts in this field of medicine.

Until the publication of *Peripheral Nerve Injuries* one had to depend upon the old British Research Council Publication which contained to some extent, out-dated and incomplete information in a poorly illustrated, paper bound volume. It is no wonder, then, that *Peripheral Nerve Injuries* by Haymaker and Woodhall is unconditionally recommended as the source-book on the diagnosis of peripheral nerve injuries. It will be of great worth to anyone confronted with a problem in this field.

R. M. N. C.

Electrocardiography. By E. GREY DIMOND, M.D., Professor and Chairman, Department of Medicine and Director of Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City. 261 pages; 21.5 × 28.5 cm. The C. V. Mosby Company, St. Louis. 1954. Price, $14.00.

So many are the volumes published on the subject of electrocardiography, that a new one must be judged not only with regard to its author's objectives and how well they are fulfilled, but with respect to how it accomplishes this purpose in comparison with existing texts.

"This book has been written solely for the general practitioner and the medical student with the intent of carrying such an audience from the totally uninitiated stage to a fairly sophisticated level."

The introductory section deals with instrumentation, technic and theory in an adequate fashion. The second portion is devoted to hypertrophy, bundle branch block, myocardial disease, congenital heart disease, arrhythmias, and electrolytes, etc. These discussions are poorly balanced, with a fairly detailed clinical, x-ray and electrocardiographic description of congenital heart disease, and a briefer and inadequate presentation of myocardial infarction.

The author correctly states that "to own the machine is not enough; the physician is obligated to use his machine correctly and interpret the record." Unfortun-

ately, study of this text will not equip him properly to discharge the latter responsibility, nor does it do this as well as other less expensive volumes which are available.

S. S.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Anatomy of the Human Body. 26th Ed. By HENRY GRAY, F.R.S., Late Fellow of the Royal College of Surgeons, etc.; 26th Edition edited by CHARLES MAYO GOSS, M.D., Managing Editor of the Anatomical Record, etc. 1,480 pages; 26.5 × 17.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $16.00.

Cancer: Race and Geography. Some Etiological, Environmental, Ethnological, Epidemiological, and Statistical Aspects in Caucasoids, Mongoloids, Negroids, and Mexicans. By PAUL E. STEINER, Ph.D., M.D., Professor of Pathology, The University of Chicago, Chicago, Ill. 363 pages; 23.5 × 15.5 cm. 1954. The Williams & Wilkins Co., Baltimore. Price, $5.00.

Cerebrovascular Disease. By JAMES PETER MURPHY, M.D., Assistant Clinical Professor of Neurological Surgery, George Washington University School of Medicine; Foreword by PERCIVAL BAILEY, M.D. 408 pages; 23.5 × 15.5 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, $12.00.

The Digital Circulation. By MILTON MENDLOWITZ, M.D., F.A.C.P., Associate Attending Physician, Mount Sinai Hospital, etc. 182 pages; 26 × 17.5 cm. 1954. Grune & Stratton, New York. Price, $6.75.

Diseases of the Skin. 8th Ed. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology Emeritus, University of Illinois, etc.; and HAMILTON MONTGOMERY, M.D., M.S., Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota, etc. 1,503 pages; 25.5 × 16 cm. 1954. Lea & Febiger, Philadelphia. Price, $22.00.

Heart: A Physiologic and Clinical Study of Cardiovascular Diseases. 2nd Ed. By ALDO A. LUISADA, M.D., Associate Professor of Medicine and Director, Division of Cardiology at The Chicago Medical School, under a Teaching Grant of the National Heart Institute, U. S. Public Health Service, etc.; with a Foreword by HERRMAN L. BLUMGART, Physician-in-Chief, Beth Israel Hospital, etc. 680 pages; 26 × 17.5 cm. 1954. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Hypertension: Humoral and Neurogenic Factors. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MARGARET P. CAMERON, M.A., A.B.L.S.; assisted by JOAN ETHERINGTON. 294 pages; 21 × 14 cm. 1954. Little, Brown & Company, Boston. Price, $6.75.

The Kidney. Ciba Foundation Symposium Arranged Jointly with the Renal Association. Editor for the Renal Association: A. A. G. LEWIS, B.Sc., M.D., M.R.C.P.; Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; assisted by JOAN ETHERINGTON. 333 pages; 21 × 14 cm. 1954. Little, Brown & Company, Boston. Price, $6.00.

Laboratory Techniques in Rabies: World Health Organization Monograph Series No. 23. Contributors: D. D'ANTONA, P. ATANASIU, R. BÉQUIGNON, E.

FALCHETTI, KARL HABEL, GEORGE A. HOTTLE, HARALD N. JOHNSON, MARTIN M. KAPLAN, A. KOMAROV, HILARY KOPROWSKI, PIERRE LÉPINE, THOMAS F. SELLERS, ERNEST S. TIERKEL and C. VIALAT. 150 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $3.00.

Lehrbuch der Inneren Medizin. Zweiter Band. 3. Verbesserte Auflage. By M. BROGLIE, Neumünster; H. DENNIG, Stuttgart; K. HANSEN, Lübeck; W. GRONEMEYER, Bad Lippspringe; F. GROSSE-BROCKHOFF, Bonn; N. HENNING, Erlangen; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG; G. SCHALTENBRAND, Würzburg; and H. SCHULTEN, Köln. Herausgegeben von HELMUT DENNIG, Stuttgart. 1,042 pages; 24.5 × 18 cm. 1954. Georg Thieme Verlag, Stuttgart. Price, DM 49.80.

Lehrbuch der Inneren Medizin. Erster Band. 3. Verbesserte Auflage. By M. BROGLIE, Neumünster; H. DENNIG, Stuttgart; K. HANSEN, Lübeck; W. GRONEMEYER, Bad Lippspringe; F. GROSSE-BROCKHOFF, Bonn; N. HENNING, Erlangen; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG; G. SCHALTENBRAND, Würzburg; and H. SCHULTEN, Köln. Herausgegeben von HELMUT DENNIG, Stuttgart. 1,048 pages; 24.5 × 17.5 cm. 1954. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Band I, Ganzleinen DM 49.80.

Lehrbuch der Speziellen Pathologischen Anatomie. Begründet von DR. EDUARD KAUFMANN; 11. und 12. Auflage herausgegeben von PROF. DR. MARTIN STAEMMLER. 320 pages; 25.5 × 17.5 cm. (paper-bound). 1954. Walter de Gruyter & Co., Berlin. Price, geh. DM 42.—

Metabolic Interrelations, with Special Reference to Calcium: Transactions of the Fifth Conference, New York, N. Y., January 5–6, 1953. Edited by EDWARD C. REIFENSTEIN, JR., Director, Biological and Therapeutic Research, Schering Corporation, Bloomfield, New Jersey; Editorial Assistants: SHIRLEY L. WELLS, M.S., and BEVERLY B. TURNER. 386 pages; 24 × 15.5 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $5.00.

Mycobacterium Balnei: A New Acid-Fast Bacillus Occurring in Swimming Pools and Capable of Producing Skin Lesions in Humans. (Acta Tuberculosea Scandinavica Supplementum XXXIII.) By FOLKE LINELL, Professor of Pathology, University of Lund, Sweden; and ÅKE NORDÉN, Assistant Professor of Medicine, University of Lund, Sweden. 84 pages; 24.5 × 17 cm. (paper-bound). 1954. Ejnar Munksgaard, Copenhagen. Price, Danish kr. 16, plus postage.

Of Publishing Scientific Papers. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, New Orleans, Louisiana. 40 pages; 25.5 × 20.5 cm. (loose-leaf binding). 1954. Grune & Stratton, New York. Price, $2.75.

The Physician and His Practice. Edited by JOSEPH GARLAND, M.D., Editor, *The New England Journal of Medicine.* 270 pages; 21 × 14 cm. 1954. Little, Brown and Company, Boston. Price, $5.00.

Das Postthrombotische Syndrom. By DR. MED. TH. HALSE. 114 pages; 23.5 × 16 cm. (paper-bound). 1954. Verlag Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 18; geb. DM 20.

Proceedings of the Fourth International Congress of the International Society of Hematology, Mar del Plata, Argentina—September 20–27, 1952. Associate

Editors: F. JIMENEZ DE ASUA, Buenos Aires; WILLIAM DAMESHEK, Boston; and SOL HABERMAN, Dallas; Advisory Editors: JEAN BERNARD, Paris; P. INTROZZI, Pavia; O. P. JONES, Buffalo; SVEN MOESCHLIN, Zurich; and L. M. TOCANTINS, Philadelphia; Assistant Editors: GONZALO E. APONTE, Philadelphia; and JORGE LAJOUS, Buenos Aires. 473 pages; 26 × 18 cm. 1954. Grune & Stratton, New York. Price, $10.00.

Report of the Medical Research Council for the Year 1952–1953. Committee of Privy Council for Medical Research. Presented by the LORD PRESIDENT OF THE COUNCIL to Parliament by Command of Her Majesty, June, 1954. 269 pages; 24.5 × 15 cm. (paper-bound). 1954. Her Majesty's Stationery Office, London. Price, 7s 6d net.

Report of the Ontario Health Survey Committee. Volumes I, II and III. 450 pages; 29 × 22 cm. 1954. Published under the Authority of the Minister of Health for Ontario, Toronto. No charge.

Roentgen-Diagnostics. Volume IV: Gastrointestinal Tract, Gynecology, Urology. First American Edition (Based on the Fifth German Edition). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, E. UEHLINGER; English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 946 pages; 28 × 19.5 cm. 1954. Grune & Stratton, New York. Price, $50.00.

Roentgen-Diagnostics: Cumulative Index. First American Edition (Based on the Fifth German Edition). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, E. UEHLINGER; English translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E. (Camb.), Professor of Radiology Emeritus, Northwestern University Medical School, Chicago. 103 pages; 28 × 19 cm. 1954. Grune & Stratton, New York. Price, $10.00.

Shock and Circulatory Homeostasis: Transactions of the Third Conference, September 14, 15 and 16, 1953, Princeton, N. J. Edited by HAROLD D. GREEN, M.D., Professor of Physiology and Pharmacology, and Associate in Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. 230 pages; 24 × 16 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.50.

Textbook of Pediatrics. 6th Ed. Edited by WALDO E. NELSON, M.D., Professor of Pediatrics, Temple University School of Medicine, etc.; with the collaboration of seventy contributors. 1,581 pages; 26 × 18 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $15.00.

Therapie der Lungentuberkulose. Bearbeitet von PROF. DR. E. HESSE; DOZ. DR. ST. J. LEITNER and DR. H. W. ROTH; DOZ. DR. H. WISSLER, and DOZ. DR. B. FUST. 556 pages; 23.5 × 16 cm. 1954. Medizinischer Verlag Hans Huber, Bern; exclusive representative for U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, $15.00.

Transactions of the 13th Conference on the Chemotherapy of Tuberculosis, Held on February 8 to 11, 1954, at the St. Louis Medical Society, St. Louis, Missouri, by the Veterans Administration: Army: Navy, with the Coöperation of the National Tuberculosis Association. 442 pages; 26 × 20 cm. (paper-bound). 1954. Prepared and edited by the Veterans Administration Area Medical Office, St. Louis, Mo., and the Department of Medicine and Surgery, Central Office, Washington, D. C. Price: Copies are not available for sale to individuals; a limited number may be obtained free of charge for libraries by addressing a request to Department of Medicine and Surgery, Veterans Administration, Washington, 25, D. C.

COLLEGE NEWS NOTES

Meetings, A.C.P. Committees and Board of Regents

All standing Committees of the American College of Physicians will meet at the College Headquarters, Philadelphia, November 12–13, 1954, and the Board of Regents on November 14, 1954.

Proposals of candidates received up to September 13 will be reviewed by the Committee on Credentials and passed on by the Board of Regents. Proposals received after September 13 will not be acted upon until the meeting of the Committee on Credentials in March, 1955.

Nominations for candidates for the Mead Johnson Postgraduate Scholarships were closed on October 1, 1954, according to regulations.

Application for the A. Blaine Brower Traveling Scholarship and the Elizabeth Archbold Bowes Traveling Scholarship closed on October 15, according to regulations.

A.C.P. Postgraduate Courses

In the advertising pages in this issue will be found a schedule of the College Postgraduate Courses for the Autumn of 1954. The first four courses will have been concluded by the time of the appearance of this issue. Courses No. 5, SELECTED SUBJECTS IN INTERNAL MEDICINE, at the University of Pittsburgh School of Medicine, October 25–30, No. 6, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, at the University of Pennsylvania Graduate School of Medicine, November 1–5, No. 7, INTERNAL MEDICINE, at the Beth Israel Hospital, Boston, November 8–12, No. 8, GASTROENTEROLOGY, at the University of Pennsylvania Graduate School of Medicine, November 8–12, and No. 9, A SURVEY OF RECENT DEVELOPMENTS IN THE CARDIOVASCULAR FIELD, at the Michael Reese Hospital, Chicago, December 6–11, are still open for registration, but applications should be filed promptly.

The A.C.P. Committee on Postgraduate Courses will announce the specific Postgraduate Course Program for the first half of 1955 immediately after their meeting on November 13. The contemplated courses include:

DISEASES OF THE BLOOD VESSELS AND THROMBOEMBOLIC CONDITIONS: New York Hospital, New York City; Irving S. Wright, M.D., F.A.C.P., Director; March 14–18, 1955.

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: Bunts Educational Institute of the Cleveland Clinic Foundation; A. Carlton Ernstene, M.D., F.A.C.P., Director; April 4–9.

STRESS AND AGING: Lankenau Hospital, Philadelphia; Edward L. Bortz, M.D., F.A.C.P., Director; April 20–23.

SELECTED SUBJECTS IN INTERNAL MEDICINE: Mayo Clinic, Rochester; Edgar V. Allen, M.D., F.A.C.P., et al., Directors; May 9–13.

FUNDAMENTAL ADVANCES IN INTERNAL MEDICINE: University of Colorado School of Medicine, Denver; James J. Waring, M.D., M.A.C.P., Charley J. Smyth, M.D., F.A.C.P., and Gordon Meiklejohn, M.D., (Associate), Co-directors; June 13–17.

ELECTROCARDIOGRAPHY: Massachusetts General Hospital; Conger Williams, M.D., (Associate), Director; one week, date to be announced.

RHEUMATIC DISEASES: Massachusetts General Hospital; Walter Bauer, M.D., F.A.C.P., Director; one week, date to be announced.

THE EARLY RECOGNITION OF DISEASE AND ITS PREVENTION: University of Pennsylvania School of Medicine: John P. Hubbard, M.D., Director; one week, date to be announced.

Coming A.C.P. Regional Meetings

NEW ENGLAND (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Eastern Canada), Hartford, October 22, 1954.
WESTERN PENNSYLVANIA, Pittsburgh, October 27, 1954.
NEW JERSEY, Newark, November 3, 1954.
NORTHWEST (Idaho, Oregon, Washington, British Columbia, Alberta), Seattle, November 4, 1954.
WESTERN NEW YORK, Syracuse, November 19, 1954.
MICHIGAN, Grand Rapids, December 4, 1954.
DELAWARE, Wilmington, February 5, 1955.
SOUTHERN CALIFORNIA, San Diego, February 12–13, 1955.
VIRGINIA, Richmond, February 24, 1955.
SOUTHERN ILLINOIS, Peoria, March —, 1955.
KANSAS, Wichita, March 18, 1955.

Charter Members of the American College of Physicians

The American College of Physicians was chartered on May 11, 1915. Of the members that were officially elected in 1915, there remains but one Fellow, Dr. Henry F. Quackenbos, West Palm Beach, Fla. Dr. Quackenbos was born in 1848.

Of those that were elected in 1916, the following are still living:

Dr. Raymond Clark, Brooklyn, N. Y.—born, 1870.
Dr. LeGrand Kerr, Sayville, N. Y.—born, 1870.
Dr. Leon Theodore LeWald, New York, N. Y.—born, 1874.
Dr. William Johnston Mallory, Lovettsville, Va.—born, 1874.
Dr. Marshall Carleton Pease, Ridgefield, Conn.—born, 1879.
Dr. Francis Marion Pottenger, Sr., M.A.C.P., Monrovia, Calif.—born, 1869.
Dr. J. Russell Verbrycke, Jr., Washington, D. C.—born, 1885.

Dr. Johannes H. M. A. von Tiling, Cliff Island, Maine, born, 1875, was elected an Associate of the College in 1916. Associates elected prior to 1927 had the privilege of retaining that status indefinitely and were not under obligation to qualify for Fellowship.

The list of living members elected in the early years of the College is fast dwindling. Of those elected in 1917, only the following remain:

Dr. Lester Betts, Schenectady, N. Y.—born, 1874.
Dr. Roland Cummings, Los Angeles, Calif.—born, 1879.
Dr. Robert F. Ives, Brooklyn, N. Y.—born, 1870.
Dr. Ross Moore, Los Angeles, Calif.—born, 1873.
Dr. Jesse M. W. Scott, Schenectady, N. Y.—born, 1872.
Dr. Alvin Woodward Sherrill, Pittsburgh, Pa. (Associate)—born, 1872.
Dr. George Thomas Strodl, New York, N. Y.—born, 1880.
Dr. Charles Edwin Teeter, Newark, N. J.—born, 1873.
Dr. William Cooper Voorsanger, San Francisco, Calif.—born, 1876.
Dr. Walter Wessels, Los Angeles, Calif.—born, 1880.
Dr. C. Stuart Wilson, Detroit, Mich.—born, 1884.

DISTRIBUTION OF MEMBERSHIP

(Masters, Fellows and Associates)

AMERICAN COLLEGE OF PHYSICIANS

July 30, 1954

Rank	State or Province	No. of Members	Rank	State or Province	No. of Members
1	New York	1,313	38	Mississippi	33
2	California	702	39	Maine	32
3	Pennsylvania	627	40	Manitoba, Can.	32
4	Illinois	424	41	Rhode Island	30
5	Ohio	351	42	Montana	28
6	Texas	316	43	Puerto Rico	28
7	Michigan	293	44	Delaware	27
8	Massachusetts	279	45	Utah	23
9	New Jersey	250	46	British Columbia, Can.	22
10	District of Columbia	207	47	New Hampshire	22
11	North Carolina	175	48	Hawaii	21
12	Virginia	174	49	Alberta, Can.	20
13	Maryland	171	50	New Mexico	20
14	Florida	171	51	North Dakota	20
15	Minnesota	168	52	Vermont	18
16	Connecticut	159	53	New Brunswick, Can.	12
17	Missouri	156	54	Idaho	11
18	Tennessee	141	55	Mexico	11
19	Wisconsin	136	56	South Dakota	8
20	Georgia	133	57	Cuba	8
21	Colorado	120	58	Nova Scotia, Can.	8
22	Indiana	119	59	Nevada	7
23	Louisiana	115	60	Canal Zone & Panama	7
24	Washington	97	61	Saskatchewan, Can.	7
25	Kentucky	92	62	England	6
26	Oklahoma	91	63	Wyoming	4
27	Oregon	77	64	Central America	3
28	Ontario, Can.	77		France	2
29	Nebraska	74		India	2
30	Iowa	72		Prince Edw. Island, Can.	2
31	Kansas	72		Belgium	1
32	Alabama	71		Japan	1
33	West Virginia	68		Lebanon	1
34	Arizona	65		Newfoundland, Can.	1
35	Quebec, Can.	60		Netherland Indies	1
36	South Carolina	47		Portugal	1
37	Arkansas	40		Switzerland	1
				Turkey	1

Total 8,185

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College acknowledges with gratitude the following autographed books that have been presented to the College Library of Publications by Members:

William S. Collens, M.D. (Associate), Brooklyn, N. Y.—*Peripheral Vascular Diseases* (2nd Edition), with Nathan D. Wilensky, M.D. (Associate)

Charles L. Steinberg, M.D., F.A.C.P., Rochester, N. Y.—*Arthritis and Rheumatism—The Diseases and Their Treatment.*

T. Royle Dawber, M.D., F.A.C.P., Framingham, Mass.—*Diseases of the Chest,* with Lloyd E. Hawes, M.D.

Wilfred Dorfman, M.D., F.A.C.P., Brooklyn, N. Y.—*Overweight is Curable,* (2nd Edition) with Doris Johnson, M.S.

The James Alexander Miller Fellowship for Research in Tuberculosis and Allied Problems

The New York Tuberculosis and Health Association announces that a fellowship will be available from July 1, 1955, to June 30, 1956. Dr. James Alexander Miller was a Master of the American College of Physicians and served as President, 1935–36.

The Miller Fellowship is designed to support a qualified investigator in medical or biological sciences who will devote full time to a research project in tuberculosis or allied problems. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice; and that he will be provided with the facilities necessary for the pursuit of the work.

The annual stipend will be $5,000.00. Consideration will be given for renewal of the Fellowship for one or more years.

Applications should be submitted in duplicate by Nov. 1, 1954. Application forms will be supplied on request. Address—The New York Tuberculosis and Health Association, 386 Fourth Ave., New York 16, N. Y. Awards will be announced Dec. 15, 1954.

Conference on Silicosis and Occupational Chest Diseases

A Conference on Silicosis and Occupational Chest Diseases, jointly sponsored by the McIntyre Research Foundation of Toronto, Canada, and the Saranac Laboratory of Saranac Lake, N. Y., has been arranged for Monday, Tuesday, and Wednesday, Feb. 7, 8, and 9, 1955, in the Town Hall at Saranac Lake.

Both of these organizations have for many years been conducting research along parallel lines. It is a significant development in the field of research that they have decided to pool their resources for this conference. The papers to be presented in the five full sessions will all report on original work conducted or sponsored by either the McIntyre Research Foundation or the Saranac Laboratory. In addition there will be papers presented by guest lecturers.

Doctors, scientists, and businessmen concerned with the problems of occupational chest diseases in all parts of the United States, Canada, and foreign countries are invited to attend.

Dr. Anthony J. Lanza, F.A.C.P., formerly Director of the Institute of Industrial Medicine and now Emeritus Professor of Industrial Medicine at New York University-Bellevue Medical Center, has been named Chairman of the Conference. He is also Chairman of the Scientific Program Committee, which comprises Dr. Dudley Irwin, Medical Director, Aluminum Company of America, Pittsburgh, Pa.; Dr. Guy Hannon, Medical Director, McIntyre Research Foundation, Washington, Pa.; Dr. Gordon M. Meade (Associate), Executive Director of Trudeau-Saranac Institute; and Dr. Gerrit W. H. Schepers, Director of the Saranac Laboratory.

The business arrangements, including reservations, will be handled by Norman R. Sturgis, Jr., and the Treasurer will be Clarence L. Wagner, both of the Trudeau-Saranac Institute staff. All communications concerning the conference should be addressed to Mr. Sturgis, Saranac Laboratory, Saranac Lake, N. Y.

College of Physicians and Surgeons of South Africa Being Organized

A College of Physicians and Surgeons is being organized in South Africa, according to a recent communication. It will include several faculties and its membership will be similar to the Associate membership of the American College of Physicians. However, Fellowship in either medicine or surgery will be subject to recommendation to the Council of the College by the Examination and Credentials

Committee after examination at the highest possible level consistent with equity and at a standard not less than that of M.R.C.P. or F.R.C.S. In medicine it is predicted they will follow the Edinburgh system. A candidate must show a high standard of knowledge in internal medicine and therapeutics as well as the knowledge of a specialist in a selected department of medicine.

Continuation Course in Infectious Diseases

The University of Minnesota announces a Continuation Course in Infectious Diseases for General Physicians which will be held at the Center for Continuation Study Nov. 18–20. Practical and fundamental aspects of the diagnosis and management of infectious diseases of all types will be taken up. Guest speakers will be Drs. Harry Eagle, Chief, Section of Experimental Therapeutics, National Microbiological Institute, National Institutes of Health, Bethesda, Md.; and Ellard M. Yow, Assistant Professor of Medicine, Baylor University School of Medicine, Houston, Tex. Dr. Eagle will also present the annual Journal-Lancet Lecture on Thursday evening, Nov. 18. The course will be presented under the direction of Dr. W. W. Spink, F.A.C.P., Professor, Department of Medicine; members of the faculty of the University of Minnesota Medical School and the Mayo Foundation will complete the faculty. Lodging and meal accommodations are available at the Center for Continuation Study.

Announcement of the Van Meter Prize Award

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held in Oklahoma City, Okla., April 28, 29 and 30, 1955, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length, must be presented in English, and a typewritten, double-spaced copy in duplicate sent to the Secretary, John C. McClintock, M.D., 149½ Washington Ave., Albany, N. Y., not later than Jan. 15, 1955. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

Future Meetings, American Academy of General Practice

The American Academy of General Practice has set the following dates for the Annual Scientific Assembly of that organization:

1955 Assembly: March 28 to 31, Los Angeles
1956 Assembly: March 26 to 29, Washington, D. C.
1957 Assembly: March 25 to 28, St. Louis

Fall Tuberculosis Conference, Philadelphia Tuberculosis and Health Association

The Fall Tuberculosis Conference of the Philadelphia Tuberculosis and Health Association will be held at the Bellevue Stratford Hotel, Philadelphia, on Monday, November 1. Dr. Winthrop N. Davey of the University of Michigan will discuss "Indications or Contra Indications for Cortisone Therapy in Patients with Pul-

monary Disease," and his presentation will be discussed by Dr. David A. Cooper, F.A.C.P., Philadelphia. Dr. Philip A. Tumulty of St. Louis University School of Medicine will present a paper on "Pulmonary Manifestations of Systemic Lupus," which will be discussed by Dr. Garfield Duncan, F.A.C.P., Philadelphia. Dr. W. Edward Chamberlain, F.A.C.P., of Philadelphia will moderate a panel on "Management of Tuberculosis in Private Practice"; the panel of experts will include Drs. J. Antrim Crellin, F.A.C.P., Leon Collins, F.A.C.P., and John T. Farrell, F.A.C.P., all of Philadelphia. At a luncheon session Dr. David A. Cooper, F.A.C.P., will preside, and Dr. John H. Skavlem, F.A.C.P., President of the National Tuberculosis Association, will be the speaker of the day.

On the afternoon program appears the following: "Problems in the Tuberculosis Control Program"; Moderator, Dr. Martin J. Sokoloff, F.A.C.P.; panelists—Drs. Esmond R. Long, F.A.C.P., Philadelphia, Henry P. Close, F.A.C.P., Philadelphia, Peter Theodos, Philadelphia, and Morrison C. Stayer, Harrisburg. The program will be concluded by Dr. Cuyler Hammond of the American Cancer Society, who will present current studies into the cause of lung cancer, his paper to be discussed by Dr. Katharine Boucot.

The Association states that it is apparent that the general practitioner is going to be involved in the actual treatment of the tuberculosis patient to a much greater extent than he has in the recent past, and that fewer patients will be treated by specialists in chest diseases. For this reason the above program is aimed primarily at the private physician in general practice.

Dr. Benjamin B. Wells, F.A.C.P., formerly Professor of Medicine at the University of Arkansas School of Medicine, has accepted an appointment as Professor of Medicine at the Creighton University School of Medicine, Omaha, as of the beginning of the current semester. Dr. Wells continues as a consulting editor with the W. B. Saunders Company, Medical Book Publishers, Philadelphia.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., was the guest of honor at a dinner meeting of the West Virginia Medical Licensing Board, held July 12 at the Daniel Boone Hotel in Charleston. Dr. Frank J. Holroyd, F.A.C.P., Princeton, presented a plaque bearing facsimile signatures of all the members of the Board to Dr. Vest "in grateful appreciation of twenty years' service on the Medical Licensing Board of West Virginia." A Fellow of the College since 1919 and former Governor for West Virginia, Dr. Vest has also served as President of the West Virginia State Medical Association and of the Southern Medical Association.

Drs. Madelaine Ray Brown, F.A.C.P., and Priscilla White, F.A.C.P., both of Boston, recently received two of the Elizabeth Blackwell Citations in ceremonies held at the New York Infirmary. Dr. Brown is co-author of the first published description of the syndrome of muscular paralysis due to kidney disease, and Dr. White, who has made studies of diabetes in pregnancy, is also co-author of the textbook *Treatment of Diabetes Mellitus* and author of *Diabetes in Childhood and Adolescence*.

Dr. Cyrus C. Sturgis, Ann Arbor, Mich., President of the American College of Physicians, received the honorary degree of Doctor of Science from Emory University during its Centennial Celebration at Atlanta, Ga., Oct. 4–5, 1954.

Dr. Walter P. Anderton, F.A.C.P., New York City, was recently reëlected Secretary of the Medical Society of the State of New York, and Dr. Maurice J. Dattelbaum, F.A.C.P., Brooklyn, was appointed Treasurer.

Dr. W. Holmes Chapman, Jr., F.A.C.P., Suffolk, was elected Vice President of the Virginia State Board of Medical Examiners at its meeting in Richmond on June 16. Dr. K. D. Graves, F.A.C.P., Roanoke, was reëlected Secretary-Treasurer.

Dr. Walter L. Bierring, M.A.C.P., Des Moines, has recently received a life membership, the only one of its kind, in the Iowa Public Health Association. Dr. Bierring, a former Vice President and Regent of the College, was the State Health Commissioner of Iowa for twenty years and is now Head of the Health Department's new Division of Gerontology and Cardiac and Other Chronic Diseases.

Dr. Jesse McCall, F.A.C.P., Newton, has been elected Treasurer of the Medical Society of New Jersey.

Two Fellows of the College from New York City, Drs. Alexander B. Gutman and Russell L. Cecil, received awards at the Eleventh Annual Meeting of the American Medical Writers' Association in Chicago, Sept. 24. Dr. Gutman accepted the 1954 A.M.W.A. Honor Award for Distinguished Service in Medical Journalism on behalf of the *American Journal of Medicine*, which he edits. Dr. Cecil, who is Emeritus Professor of Medicine at Cornell University Medical College, was the recipient of the 1954 A.M.W.A. Honor Award given for distinguished contributions to medical literature. During the annual business meeting, Dr. Lee D. van Antwerp, F.A.C.P., Chicago, was installed as President.

Dr. William J. Atkinson, Jr. (Associate), Mobile, is President-Elect of the Alabama Heart Association, and Dr. Maxwell Moody, Jr. (Associate), Tuscaloosa, is one of the two new members of the Executive Board.

Dr. Daniel H. Autry, F.A.C.P., Little Rock, was elected Treasurer of the Arkansas Medical Society at its annual meeting.

Dr. Louis K. Alpert, F.A.C.P., Washington, D. C., has recently been appointed Chairman of the Committee on Detection and Education of the American Diabetes Association.

Dr. James H. Stygall, F.A.C.P., Indianapolis, is the new President-Elect of the American College of Chest Physicians. Drs. Herman J. Moersch, F.A.C.P., Rochester, Minn., and Burgess L. Gordon, F.A.C.P., Philadelphia, are First Vice President and Second Vice President, respectively.

Dr. Nils P. Larsen, F.A.C.P., Honolulu, College Governor for Hawaii, was recently elected President of the Hawaii Medical Association.

Drs. Waldo B. Moyers, F.A.C.P., Hyattsville, and Samuel Whitehouse, F.A.C.P., Baltimore, were recently elected Vice Presidents of the Medical and Chirurgical Faculty of the State of Maryland.

Dr. F. Garm Norbury, F.A.C.P., Jacksonville, was named President-Elect at the annual meeting of the Illinois State Medical Society. Drs. Louis R. Limarzi, F.A.C.P., Chicago, and J. Crescent Redington (Associate), Galesburg, were elected First Vice President and Second Vice President, respectively.

Dr. Edward J. Lefeber, F.A.C.P., Galveston, was recently elected First Vice President of the Texas Society of Gastroenterologists and Proctologists, and Dr. William T. Arnold (Associate), Houston, was chosen Secretary-Treasurer.

Dr. O. B. Mayer, F.A.C.P., Columbia, was recently chosen President-Elect of the South Carolina Medical Association.

At its annual meeting, the Oklahoma State Medical Association elected Dr. R. Q. Goodwin, F.A.C.P., Oklahoma City, President-Elect.

Dr. Harry C. Schmeisser, F.A.C.P., Memphis, has been appointed Emeritus Professor of Pathology and Bacteriology at the University of Tennessee College of Medicine and Consultant to the City of Memphis Hospitals. Dr. Schmeisser joined the staff of the School of Medicine in 1921 and has been a Fellow of the College since 1927.

Col. James S. Taylor, (MC), USA, Retired, F.A.C.P., is now Associate Professor of Medicine at the University of Arkansas School of Medicine, Little Rock.

Dr. William B. Tucker, F.A.C.P., formerly Chief of the Tuberculosis Service, Veterans Administration Hospital, Minneapolis, and Professor of Medicine, University of Minnesota Medical School, has accepted a position as Chief of the Pulmonary Disease Service, Veterans Administration Hospital, Durham, N. C., and as Professor of Medicine, Duke University School of Medicine.

Dr. Arthur J. Seaman (Associate), Portland, Ore., has been awarded a Fulbright Fellowship for study and research at the University of Oslo, Norway, during the 1954–55 academic year. Associate Professor of Experimental Medicine at the University of Oregon Medical School, Dr. Seaman will develop a project on blood coagulation under the supervision of Dr. Paul Owren, Professor of Medicine at Oslo. During the Fifth International Congress of the International Society of Hematology in Paris, Sept. 6–12, Dr. Seaman presented a paper concerning certain aspects of normal and leukemic white blood cells, which he prepared with Dr. Edwin E. Osgood, F.A.C.P., Dr. Harold Tivey, and Demetrios A. Rigas, Ph.D.

Dr. Arthur E. T. Rogers (Associate), formerly Director of the Division of Chest Diseases, City of Hope, Long Beach, Calif., is now Medical Director of Stony Brook Retreat, the tuberculosis hospital for Kern County, Keene, Calif. Dr. Rogers is also Chief of the Tuberculosis Clinic of the Kern General Hospital at Bakersfield.

Dr. James J. Waring, M.A.C.P., Denver, spent June as a special guest of the Brompton Chest Hospital in England, participating in ward rounds, clinical conferences and giving lectures on chest diseases. He spent the month of July visiting other chest institutions throughout Wales and England.

Dr. Charles M. Caravati, F.A.C.P., College Governor for Virginia, and Assistant Professor of Clinical Medicine at the Medical College of Virginia, presented a Postgraduate Course before the Medical Association of Puerto Rico at San Juan from August 9 to 13, 1954. His successive daily titles were: "Jaundice—its Differ-

ential Diagnosis"; "Hepatic Failure"; "Modern Concepts in the Management of Hepatitis and Cirrhosis"; "Gastric Ulcer"; and "Upper Gastro-intestinal Hemorrhage."

Dr. Elwyn L. Heller, F.A.C.P., Pittsburgh, recently assumed the Directorship of the Laboratory at Shadyside Hospital, Pittsburgh, having relinquished his former position as Director of Laboratories at Presbyterian Hospital, Medical Center, University of Pittsburgh. Dr. Heller, however, retains his academic appointment as Associate Professor of Pathology at the University of Pittsburgh School of Medicine.

Dr. Albert P. Knight, F.A.C.P., Washington, D. C., will spend the next two years as Assistant Co-Director (Designate), Public Health Coöperative, which acts with the Preventive Medicine Division of the Ministry of Health of Iran.

Dr. Perry J. Melnick, F.A.C.P., has removed from Los Angeles to Eloise, Mich., where he is Pathologist to the Wayne County General Hospital, Assistant Professor of Pathology at Wayne University College of Medicine, Detroit, and an Associate Editor of the American Journal of Clinical Pathology.

Dr. Thomas A. Johnson, F.A.C.P., was recently appointed Professor of Clinical Gastro-enterology in the University of Pennsylvania Graduate School of Medicine.

A.C.P. Representatives to Poliomyelitis Congress

Dr. John R. Paul, F.A.C.P., New Haven, Conn., and Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., were official representatives of the American College of Physicians to the Third International Poliomyelitis Congress at Rome, Italy, September 6–10, 1954.

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Regent and former President of the College, was the Official Representative of the American College of Physicians at the Third International Congress of Internal Medicine, at Stockholm, Sweden, Sept. 15–18. He also represented the College at the meeting of the World Medical Association at Rome.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, was appointed a member of the Scientific Advisory Board of the Tobacco Industry Research Committee, in August. The Committee, formed earlier this year by a group of cigarette manufacturers, organizations of tobacco growers and warehouse associations to sponsor objective research into all phases of tobacco use and health, is under the Directorship of Dr. Clarence Cook Little, who is also Board Chairman. Other members of the Board include Dr. Leon O. Jacobson, F.A.C.P., Chicago, Dr. Kenneth Merrill Lynch, F.A.C.P., Charleston, S. C., and Dr. Stanley P. Reimann, F.A.C.P., Philadelphia.

Dr. William C. Moloney, F.A.C.P., has been appointed Director of Clinical Laboratories at Boston City Hospital. Dr. Moloney has also resumed his position as Clinical Professor of Medicine and Assistant Director of the First and Third Medical Services (Tufts) at the Boston City Hospital after a two-year leave of absence while serving as Deputy Director of the Atomic Bomb Casualty Commission in Hiroshima, Japan.

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Secretary-General of the College, has recently been appointed a member of the Scientific and Educational Council of the American Foundation for Allergic Diseases.

Dr. Emanuel E. Mandel, F.A.C.P., resigned as a regular officer of the U. S. Public Health Service last June, as Chief of the Hematology and Biochemistry Section of the Communicable Disease Center, Public Health Service, and as Assistant Professor of Clinical Pathology and as Clinical Assistant Professor of Medicine at Emory University School of Medicine. Dr. Mandel is now full time Associate Professor of Medicine at the Chicago Medical School, with his office at the Mount Sinai Hospital in Chicago.

Dr. Abraham M. Rabiner, F.A.C.P., has recently been promoted to Professor and Head of the Division of Neurology of the Department of Medicine at the State University of New York College of Medicine at New York City.

Dr. Nathaniel B. Kurnick (Associate), former Associate Professor of Medicine, Tulane University of Louisiana School of Medicine, has recently been appointed Associate Clinical Professor of Medicine at the University of California at Los Angeles.

Dr. Thomas A. Harris (Associate) has retired from active duty in the Medical Corps of the U. S. Navy and has accepted an appointment as Associate Professor of Psychiatry at the University of Arkansas School of Medicine, Little Rock.

Dr. William B. Porter, F.A.C.P., Richmond, Va., has been appointed a member of the Advisory Medical Board in America of the American Hospital, Paris, France.

Dr. Arthur J. Vorwald, F.A.C.P., former Director of the Saranac Laboratory and the Trudeau Foundation, Saranac Lake, N. Y., was recently named Head of the newly created Department of Industrial Medicine at Wayne University College of Medicine, Detroit.

Dr. J. Edward Berk, F.A.C.P., heretofore Assistant Professor of Medicine and Research Associate, Fels Research Institute of Temple University School of Medicine, succeeded Dr. George B. Eusterman, F.A.C.P., on Sept. 1, as Chief of Medicine and Director of Medical Education at Sinai Hospital, Detroit, Mich. Dr. Berk will also be Associate Professor of Clinical Medicine at Wayne University College of Medicine. The Sinai Hospital is a new institution, only about one and a half years old. Its program is a very active one.

Dr. Alex. M. Burgess, F.A.C.P., Providence, will be the guest speaker at the annual dinner meeting at Hartford of the Connecticut Veterans Administration Medical Society on October 21, 1954. His topic will be "Boards and Shingles."

Captain I. L. V. Norman, MC, USN, F.A.C.P., on August 7 was selected to be Rear Admiral, Medical Corps, in the United States Navy. At the present time he is serving as Commanding Officer of the U. S. Naval Hospital, Great Lakes, Illinois.

Many members of the College contributed to the success of the Nineteenth Annual Meeting of the Mississippi Valley Medical Society, held in Chicago, Sept. 22–24. Dr. Leroy H. Sloan, F.A.C.P., Chicago, immediate past President of the

College, served as Moderator for a Panel on Peptic Ulcer that included Drs. Hans Popper, F.A.C.P., Chicago, and Lowell D. Snorf, Sr., F.A.C.P., Evanston, Ill. Dr. Elmer L. Sevringhaus, F.A.C.P., Essex Fells, N. J., moderated a Panel on Recent Developments in Endocrinology that included Dr. Alexander B. Gutman, F.A.C.P., New York City. Participants in the Panel on Diseases of the Heart and Blood Vessels, which was moderated by Dr. Chauncey C. Maher, Sr., F.A.C.P., Chicago, included Drs. Benjamin M. Gasul, F.A.C.P., Don C. Sutton, F.A.C.P., and Oglesby Paul (Associate), all of Chicago. Dr. Alphonse McMahon, F.A.C.P., St. Louis, was Moderator for the Panel on Hypertension, in which Drs. O. P. Joseph Falk, F.A.C.P., St. Louis, Thomas J. Coogan, F.A.C.P., and George E. Wakerlin, F.A.C.P., Chicago, participated. Individual presentations were also given by the following Chicago Fellows: Dr. Richard B. Capps, "Infectious Hepatitis"; Dr. Paul S. Rhoads, "Use and Misuse of Antibiotics in General Practice"; Dr. Henry T. Ricketts, "Common Problems in the Management of Diabetes Mellitus"; and Dr. Francis E. Senear, "Skin Lesions Commonly Seen in General Practice."

At a meeting of the International Society of Blood Transfusion, held in Paris, France, Sept. 13–19, Dr. Philip Levine, F.A.C.P., Raritan, N. J., delivered a report on "Transfusion Problems due to Rare Antibodies," and Dr. James L. Tullis, F.A.C.P., Boston, spoke on "Preservation of Platelets."

Dr. Albert M. Snell, F.A.C.P., Palo Alto, Calif., addressed the Fifth Annual Conference of the Reno (Nev.) Surgical Society, which met Aug. 19–21. His initial topic was "Ulcerative Colitis."

Dr. Howard A. Rusk, F.A.C.P., New York City, gave the principal address in a session on "Dynamic Rehabilitation" that was part of the Sixth World Congress of the International Society for the Welfare of Cripples, which convened Sept. 13–17 at The Hague, Netherlands.

In addition to the guest speakers reported in an earlier issue of this journal, Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., President of the College, discussed "Some Recent Advances in Hematology" at the West Virginia Regional Meeting of the College, which was held during the 87th Annual Meeting of the West Virginia State Medical Association, at White Sulphur Springs, Aug. 19–21. Other guest speakers at the State meeting included Dr. George F. Lull, F.A.C.P., Chicago, Secretary-General Manager of the American Medical Association, who participated in a public relations conference, and Dr. James S. Browning, F.A.C.P., Indianapolis, Ind., who spoke on "Some Emotional Factors in Rheumatic Disease" and "Some Psychosomatic Factors of Geriatrics."

Drs. Lewis Dexter, F.A.C.P., Boston, and Thomas Hale Ham, F.A.C.P., Cleveland, were among the out-of-state speakers at the 141st Annual Meeting of the Vermont State Medical Society, held in conjunction with the New Hampshire State Medical Society at Bretton Woods, N. H., Oct. 3–5. Both Dr. Ham and Dr. Dexter were general session speakers, and Dr. Dexter also participated in the Section on Internal Medicine.

Drs. Richard H. Freyberg, F.A.C.P., Sidney C. Werner, F.A.C.P., and Charles A. Ragan, Jr., F.A.C.P., all of New York City, and Lt. Col. Eddy D. Palmer, (MC), USA, F.A.C.P., Washington, D. C., were among the guest speakers at the 29th Connecticut Clinical Congress of the Connecticut State Medical Society and the Yale University School of Medicine. Dr. Freyberg spoke on "Observations Regarding

Non Hormone Therapy for Arthritis"; Dr. Werner, on "Radioactive Iodine in the Treatment of Thyroid Disease"; and Dr. Ragan, on "The Management of Rheumatoid Arthritis." Col. Palmer's topic was "Acute Upper Gastrointestinal Bleeding and the Early Use of Diagnostic Measures." The meeting was held in New Haven, Sept. 15–16.

Dr. Carl V. Moore, F.A.C.P., St. Louis, College Governor for Missouri, and Dr. G. Watson James, III (Associate), Richmond, Va., are two of the principal speakers at a Symposium on the Nutritional Aspects of Blood Formation, being held at the University of Cincinnati, Oct. 22. Dr. Richard W. Vilter, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine, is Chairman of the morning session, and Dr. Marion A. Blankenhorn, First Vice President of the American College of Physicians and Professor of Medicine at the University of Cincinnati College of Medicine, is Chairman of the afternoon session.

Among the participants in the 37th Annual Conference of the American Occupational Therapy Association, being held in Washington, D. C., Oct. 16–22, are Drs. Anthony J. Lanza, F.A.C.P., New York City, and Esmond R. Long, F.A.C.P., Philadelphia. Their respective topics are "Present Day Problems in Industrial Medicine" and "Research in Tuberculosis."

Earlier this year Dr. Long, who is Director of the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis at the University of Pennsylvania, toured Spanish hospitals and sanatoria at the invitation of the Patronato Nacional Antituberculoso, the Tuberculosis Section of the Department of Health of the Government of Spain.

The Third International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the American College of Chest Physicians under the patronage of the Spanish government, was held in Barcelona, Spain, earlier this month. Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., who is Chairman of the Council on International Affairs, spoke on "Pathogenesis and Treatment of So-Called Hypertrophic Emphysema." Among those who gave presentations concerning tuberculosis were Drs. Henry C. Sweany, F.A.C.P., Tampa, Fla., Harold G. Trimble, F.A.C.P., Oakland, Calif., Joseph A. Schwartz, F.A.C.P., San Fernando, Calif., Oscar Feinsilver, F.A.C.P., Worcester, Mass., Donald R. McKay, F.A.C.P., Buffalo, N. Y., Hollis E. Johnson, F.A.C.P., Nashville, Tenn., J. Arthur Myers, F.A.C.P., Minneapolis, Minn., and Charles E. Hamilton, F.A.C.P., Brooklyn, N. Y. Those who discussed cardiovascular diseases included Drs. William Likoff, F.A.C.P., Philadelphia, John F. Briggs, F.A.C.P., St. Paul, Minn., Wilhelm Raab, F.A.C.P., Burlington, Vt., Ray W. Kissane, F.A.C.P., Columbus, Ohio, and Hyman Fisher, F.A.C.P., Iron Mountain, Mich. Carcinoma and other tumors were discussed by Drs. David A. Cooper, F.A.C.P., Philadelphia, and Edgar Mayer, F.A.C.P., New York City. Other participants in the Congress included Drs. A. A. Carabelli, F.A.C.P., Trenton, N. J. (cytology), Alvis E. Greer, F.A.C.P., Houston, Tex. (brucellosis), Arthur M. Olsen, F.A.C.P., Rochester, Minn. (bronchiectasis), Irving B. Brick (Associate), Washington, D. C. (cirrhosis of the liver), Burgess L. Gordon, F.A.C.P., Philadelphia (cardio-respiratory function studies), and Hugh G. Whitehead, Jr., F.A.C.P., Baltimore, Md. (sarcoidosis).

Under the Chairmanship of Dr. Sidney Schnur, F.A.C.P., Houston, Tex., the Houston Chamber of Commerce sponsored its Seventh Industrial Health Conference at the Shamrock Hotel, Sept. 23–25. Those participating in a Symposium on Absenteeism, Alcoholism, and Mental Health in Industry included Dr. Norman Plummer,

F.A.C.P., New York City, "Absenteeism"; Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., "Alcoholism in Industry"; and Dr. William C. Menninger, F.A.C.P., Topeka, College Governor for Kansas, "Emotional Problems of Executives."

Dr. Thomas B. Magath, F.A.C.P., Rochester, Minn., discussed "The Rustic Nature of the Echinococcus in the U. S. A." at the Fifth International Congress of Hydatidosis in Madrid, Spain, Sept. 24-Oct. 2.

Dr. R. Carmichael Tilghman, F.A.C.P., Baltimore, College Governor for Maryland, has been appointed Associate Dean of the Johns Hopkins University School of Medicine. This will occupy only part time and will not interfere with the continuation of Dr. Tilghman's practice and other duties.

Monthly Report on A.C.P. Group Insurance Plans

Health and Accident. 3,634 members have filed applications as of September 1, 1954. Many are currently receiving weekly benefit checks. During July benefit checks were distributed totaling $10,671.46 to members who have become disabled since April 15. Additionally, checks totaling $2,921.45 were distributed last month to members who became disabled between April 15, 1953, and April 15, 1954, and whose disablement has not yet been terminated. Needless to say, these payments are proving of great assistance to these members in time of financial need.

During July the first two claims for accidental death were filed. Dr. Harris V. Lilga, F.A.C.P., Petoskey, Mich., lost his life in a drowning accident and a few days later Dr. Walter I. Werner, F.A.C.P., College Governor for New Mexico, was killed in an aircraft accident. Therefore, the Plan is paying out $10,000.00 under this provision of the Plan.

Malpractice. As previously reported, this Plan is showing a very steady growth. More than 1,000 members have subscribed. Every month notices are received of increasing rates in various locations for other malpractice plans, whereas the College Plan has stayed constant.

The College brokers are conducting an investigation of currently quoted rates in every section of the United States. As a result of this inquiry, the following information has been obtained to date:

	$5/15,000	$25/75,000	$50/150,000
California (I)			
A.C.P. Group Rate	$ 90.00	$148.50	$171.00
Calif. Group Rate	85.00	165.75	191.25
Calif. Insurance Co.	130.00	222.30	257.40
Maine			
A.C.P. Group Rate	27.00	46.17	51.03
Local Co. Rates	45.00	76.95	85.05
Western New York			
A.C.P. Group Rate	35.00	59.85	66.15
Local Co. Rates	40.00	64.85	71.15
Texas			
A.C.P. Group Rate	31.50	53.86	59.53
Local Co. Rates	38.00	64.98	71.82
Georgia			
A.C.P. Group Rate	22.50	38.47	42.52
Local Co. Rates	50.00	85.50	94.50
Colorado			
A.C.P. Group Rate	45.00	76.95	85.05
Local Co. Rates	55.00	94.05	103.95

The above comparison of rates illustrates why members of the College are asking for its Group Malpractice coverage when their present policies expire. The College brokers, The Association Service Office, will be glad to furnish the names of the companies quoting the above rates to any interested member, and is prepared to furnish detailed information for any member's particular area, where such information is available.

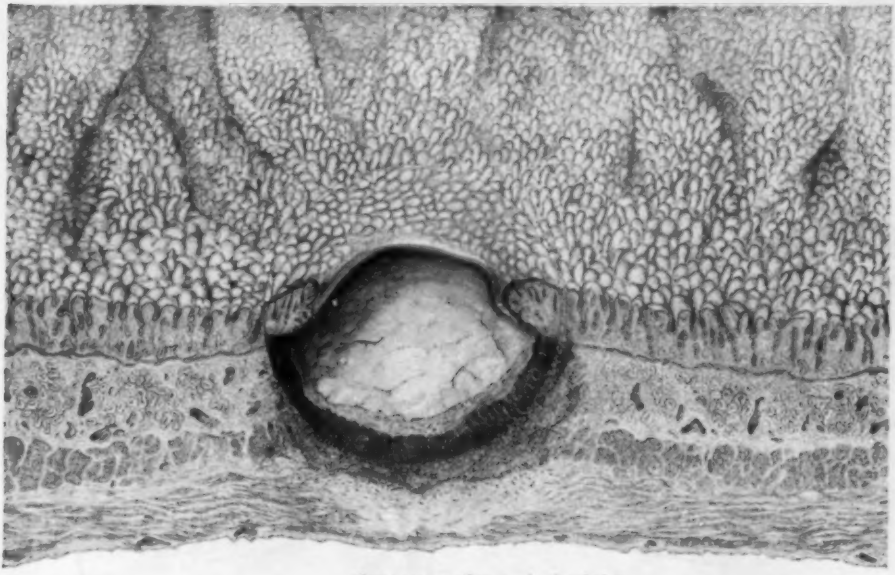
Dread Disease Plan. 1,244 members filed applications for this Plan. Several sent in applications after the closing date, July 15, and such applications had to be returned. It is expected, however, that the Plan will be reopened on June 15, 1955, giving all members who desire this type of protection an opportunity again to subscribe.

Up to date 4 claims have been filed under this Plan. They are as follows:

Texas Claim —Encephalitis —Daughter of a member.
Minnesota —Poliomyelitis—Son of a member.
New York City—Poliomyelitis—Daughter of a member.
Chicago, Ill. —Poliomyelitis—Son of a member.

Extension of Benefits to the Health and Accident Plan. The carriers of the College Group Plan for Health and Accident, The Educators Mutual Insurance Company, has just notified the College of the availability of an extension of benefits up to 10 years (instead of the present 5 years). However, certain restrictions under the 10-year Plan would be placed upon the granting of benefits to our present certificate holders. Before the conditions relating to benefits are released and before any action is taken with regard to making the extended Plan available to all members, the proposal must be approved by the College Committee on Insurance and the Board of Regents. Announcement will be made of action taken as soon as possible.

The effort to secure the extension of benefits to 10 years was undertaken because many members requested longer term benefits than 5 years. A questionnaire was sent to a large proportion of the members and about 2,000 returned the card, of whom 70% asked for a longer period of benefit payment. Rates for 10 years are just about the same as charged for 7-year Plans now in course with a limited number of other organizations. This result was obtainable because of the exceedingly favorable loss ratio of the A.C.P. Plan.



Cross section of active duodenal ulcer.

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One of the typical cases cited by the authors[2] is that of a male patient who refused surgery despite the presence of a huge crater in the duodenal bulb.

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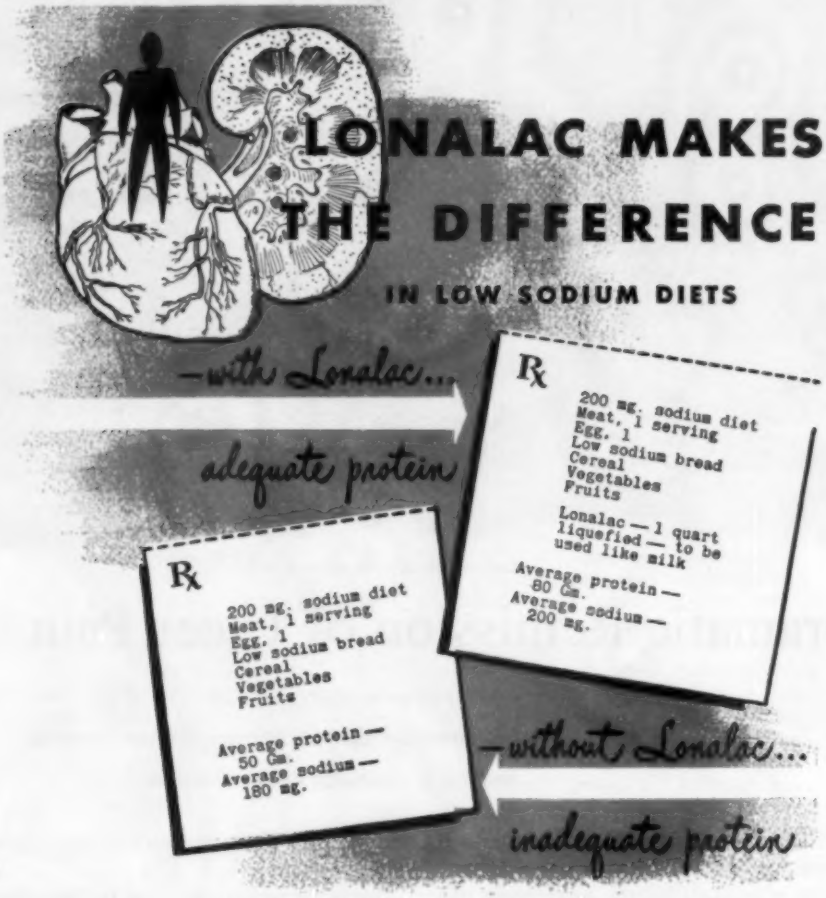
Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.
2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.



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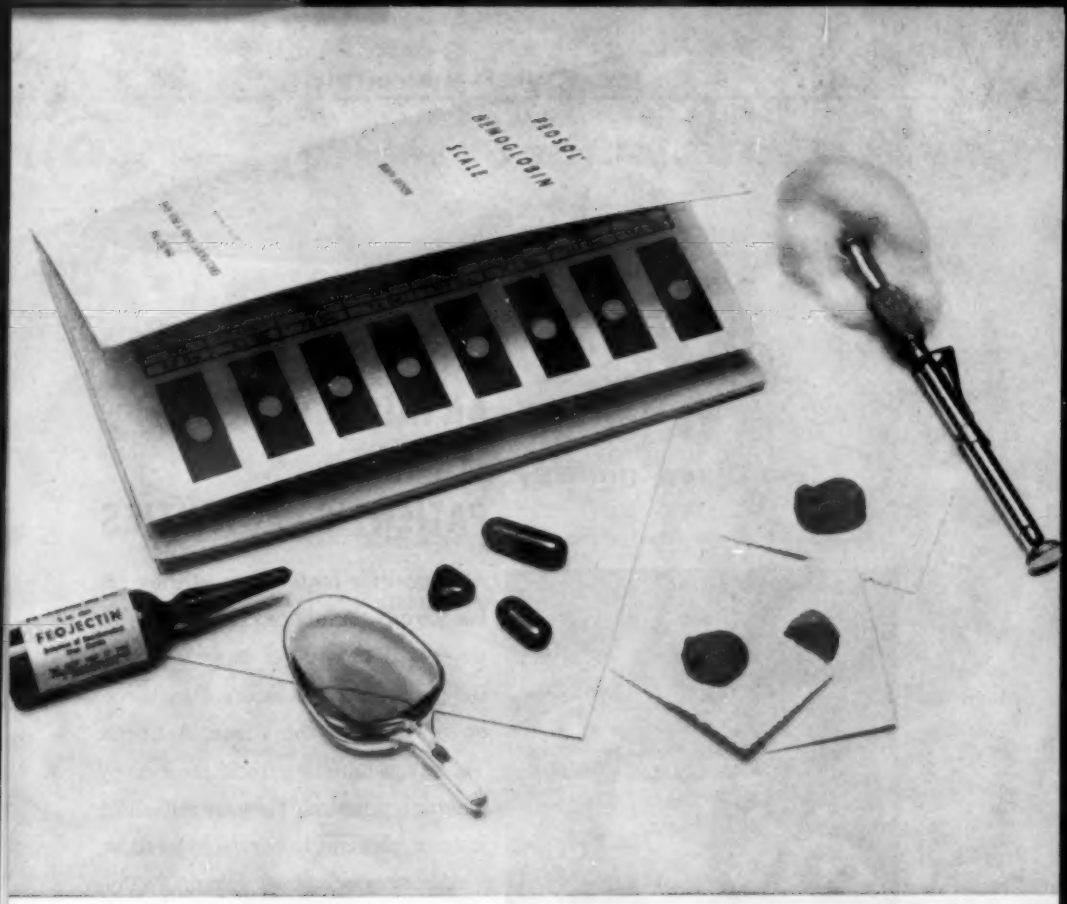

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1. Rossett, N. E., and others: Ann. Int. Med. 36:98 (Jan.) 1952

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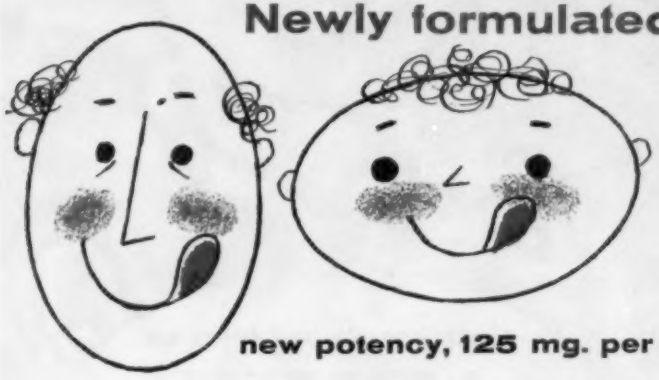

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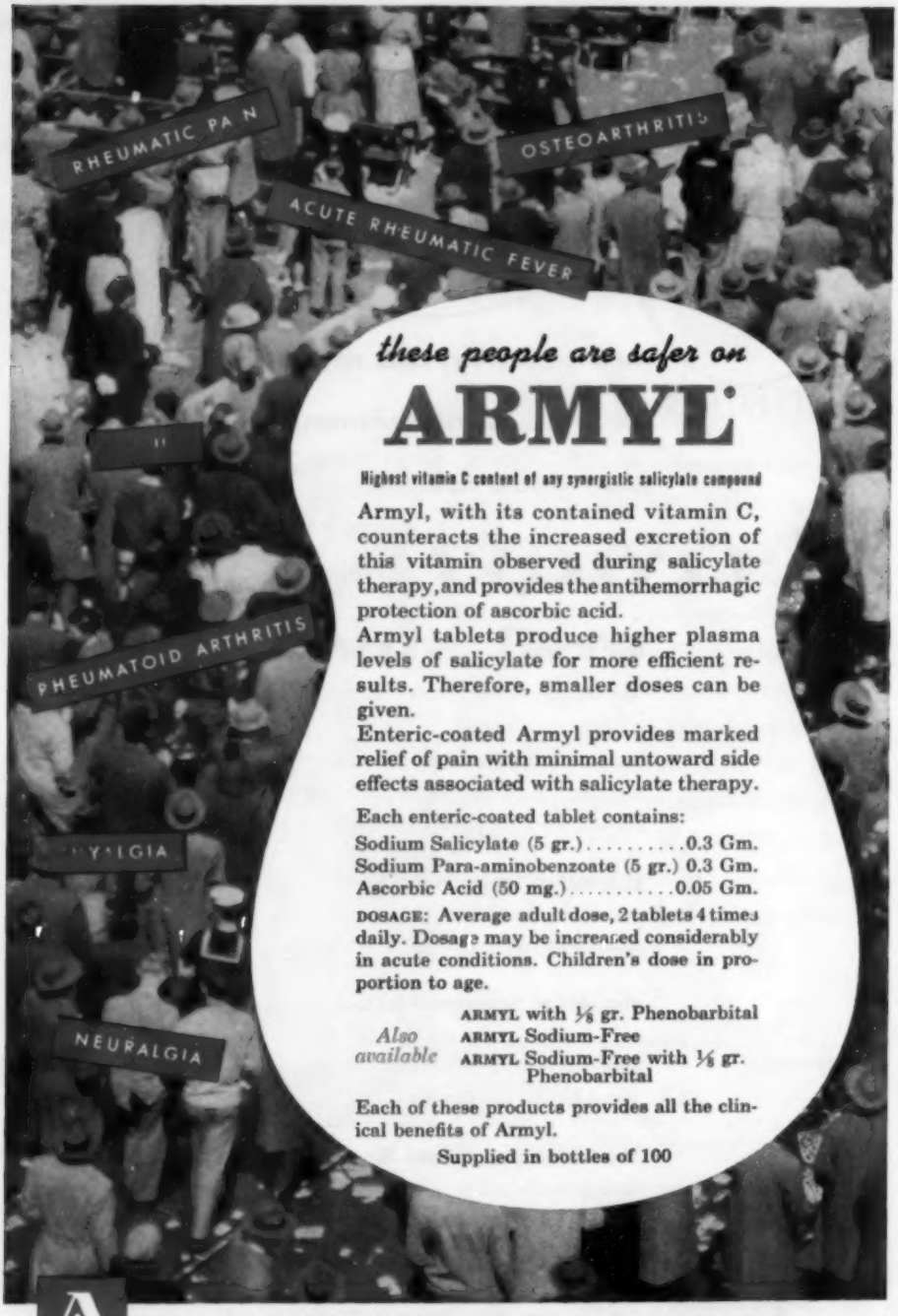

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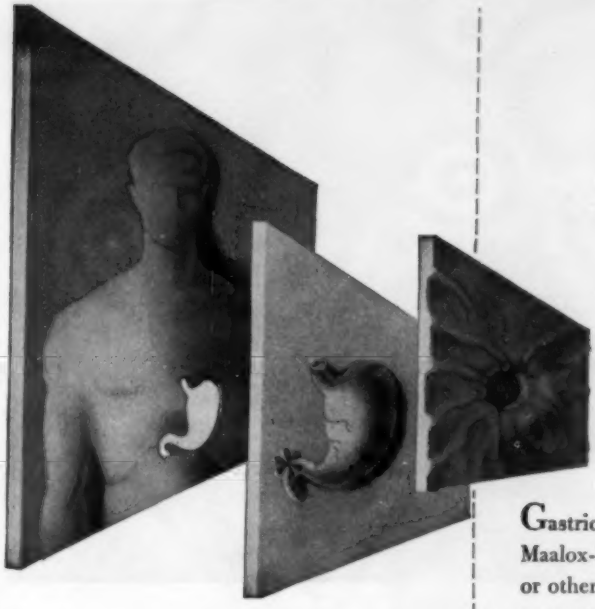

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*Fiese, M. J., and Thayer, J. M.: Archives, Int. Med. 83:132 (Jan. 1950)

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references: 1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, March 22, 1952. 2. Boland, E. W.: M. Clin. North America. Philadelphia and London. W. B. Saunders Company, March, 1954, p. 337.

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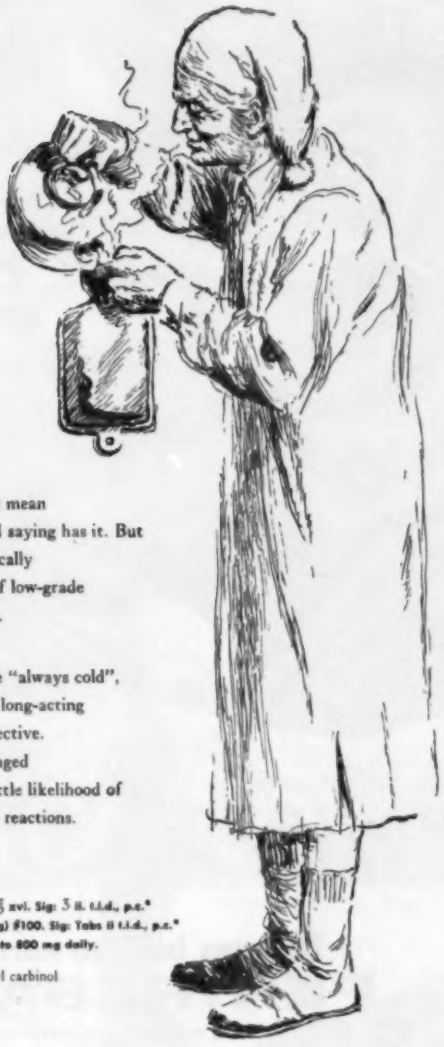

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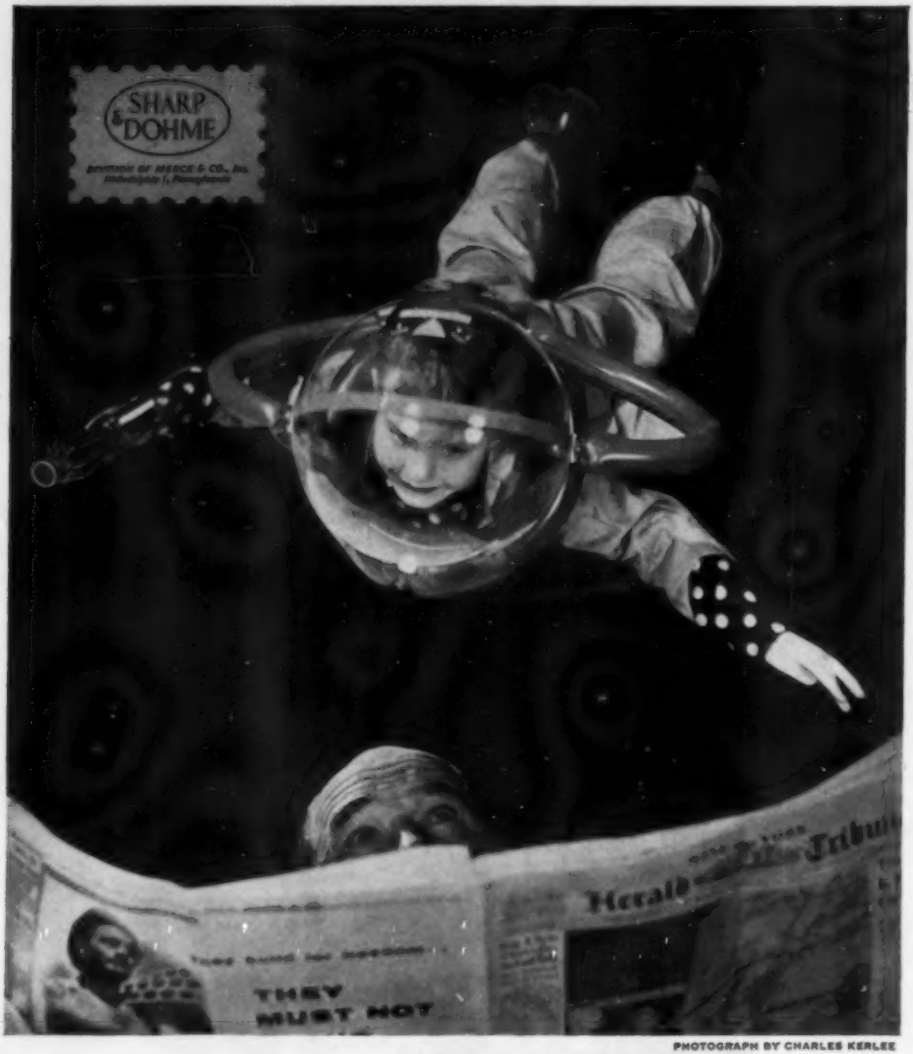

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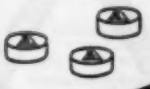

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1. ROGERS, M.P., AND GRAY, G.L.: AM. J. DIGEST. DIS. 19:180 (JUNE) 1952.

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